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A CLINICAL PATHOLOGICAL STUDY OF THE NEWBORN LUNG WITH HYALINE-LIKE MEMBRANES*

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Received for publication January 19, 1955

During the past half century, numerous papers have appeared describing a pathologic entity found in the lungs of newborn infants dying in the early neonatal period. This lesion, consisting of an eosinophilic membrane with a hyaline-like appearance lining the dilated alveoli and air ducts, and associated in most cases with atelectasis of the remaining alveoli, has been described in detail. (1, 2, 3, 4, 5, 9, 10) However, relatively few of the authors have dealt with the clinical as well as the pathologic aspects, and by those who have, different and divergent conclusions have been reached. The general subject has been previously reviewed by De and Anderson (7) and there is no need to repeat details regarding the etiology and pathogenesis. Hence, only pertinent data from the literature as it refers to the clinical status of pulmonary hyaline-like membranes in the newborn infant will be mentioned.

The purpose of this report is to present our experiences in 124 cases in which these membranes were found at autopsy. The maternal factors during pregnancy and labor will be analyzed. A system of grading the membranes, and a method of estimating the degree of atelectasis will be advanced. And finally some of the difficulties in classification encountered by the pathologist when the hyaline-like membrane is associated with other significant clinical and pathologic findings will be enumerated. In many of these instances the hyaline-like membrane was found to be incidental rather than the primary cause of the neonatal death.

THE PRESENT STUDY

During the years 1937 to 1949, inclusive, there were 26,213 live births in the weight group of 1,000 grams and over on the obstetrical service of the Johns Hopkins Hospital. In the course of this experience 480 neonatal deaths occurred among infants weighing over 1,000 grams. The lungs of 407 of the total 480 infants dying in the neonatal period were available for study (autopsy rate of 84.8 per cent). Of the 407 cases studied histologically 124 or 30.5 per cent were found to have pulmonary hyaline-like membranes. In Table I the distribution of these cases by weight increments is listed. It is apparent that pulmonary hyaline-like membranes are twice as frequent in neonatal deaths

*This investigation was supported in part by a grant from the Playtex Park Research Institute.

TABLE I

Distribution of 124 Cases of Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

Infant Weight (Grams)	Neonatal Deaths		Deaths with Hyaline Membranes	Per Cent of Neonatal Deaths	
	Total	Autopsies		Total Cases	Autopsied Cases
2500 +	167	150	26	15.6	17.3
2000–2499	78	64	30	38.5	46.9
1500–1999	110	89	34	30.9	38.2
1000–1499	125	104	34	27.2	32.7
Total Prematures	313	257	98	31.3	38.1
Total Neonatal Deaths	480	407	124	25.8	30.5

of premature infants (1,000–2,499 grams) as in full term infants (over 2,500 grams). Notice that the highest percentage of pulmonary hyaline-like membranes was 46.9 per cent in the autopsied neonatal deaths of the 2,000–2,499 gram infants. Of 563 stillbirths (fetal deaths), 382 (an autopsy per cent of 67.9 per cent) were available for study; and in this group no single case of pulmonary hyaline-like membranes was discovered. This supports the general opinion that hyaline-like membranes are not found in the lungs of stillbirths (fetal deaths). Although some experience and additional cases could be added to this study if the live born infants weighing between 400–999 grams were added it was decided for biostatistical accuracy to delete them from this investigation. However, during the years 1947 to 1949 inclusive there were 64 live born infants delivered with 52 neonatal deaths in this group. Thirteen of the 52 deaths had pulmonary hyaline-like membranes (25 per cent). In the literature there is some question as to whether the lesser weight infants have this entity.

It is necessary to point out the method by which the authors distinguished between the lungs in neonatal deaths in which hyaline-like membranes were found, and those of a group in which a certain degree of atelectasis was also associated with the membranes. An arbitrary grading system of the degree of hyaline-like membranes in the lung was necessary, (I to IV), since in some sections occasionally only a few air ducts containing hyaline-like membranes in a well expanded lung were observed and these scant findings could not be considered to be the cause of death of that particular infant. In other cases, however, with extensive hyaline-like membranes associated with a marked degree of atelectasis, the cause of death could very well be ascribed to these factors. Figure 1-A shows an area of lung with only very thin membranes, but with rather extensive atelectasis. This situation would be designated as a Grade I hyaline-like membrane. The reader should compare Figure 1-A with

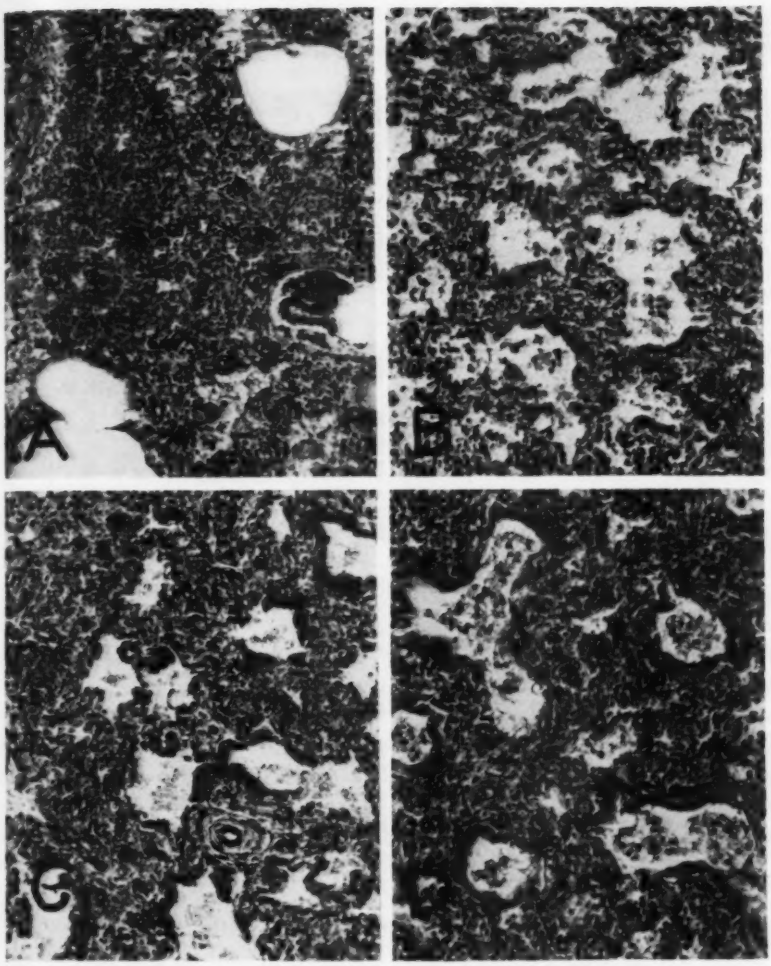

FIGURE 1—Illustrates a grading system of hyaline-like membranes.

FIG. 1-A. Photomicrograph of the lung of a 1710 gram female infant of a non complicated pregnancy except for premature rupture of membranes (39 hours). Poor at birth, with 4 minutes of resuscitation; lived 10 hours. Grade I membranes, with 90 per cent atelectasis. Hematoxylin and eosin stain (×200).

FIG. 1-B. Photomicrograph of the lung of a 1125 gram female infant. Described as poor at birth, was resuscitated and lived 2 hours and 40 minutes. Grade II membranes. Seventy per cent atelectasis. Hematoxylin and eosin stain (×200).

FIG. 1-C. Photomicrograph of the lung of a 1875 gram male infant delivered by breech extraction after a 5 hour labor. Infant cried and breathed immediately at birth. Retraction noticed. Lived 25 hours. Grade III membranes. Eighty per cent atelectasis. Hematoxylin and eosin (×200).

FIG. 1-D. Photomicrograph of the lung of a 2850 gram male infant by elective cesarean section 23 days before the E.D.C. Sodium pentothal administered for 33 minutes before delivery. Infant cried immediately at birth, temporary apnea necessitated some resuscitation. Cyanotic. Died at 39 hours. Grade IV membrane and almost 90 per cent atelectasis. Note inflammatory cells present. Hematoxylin and eosin (×200).

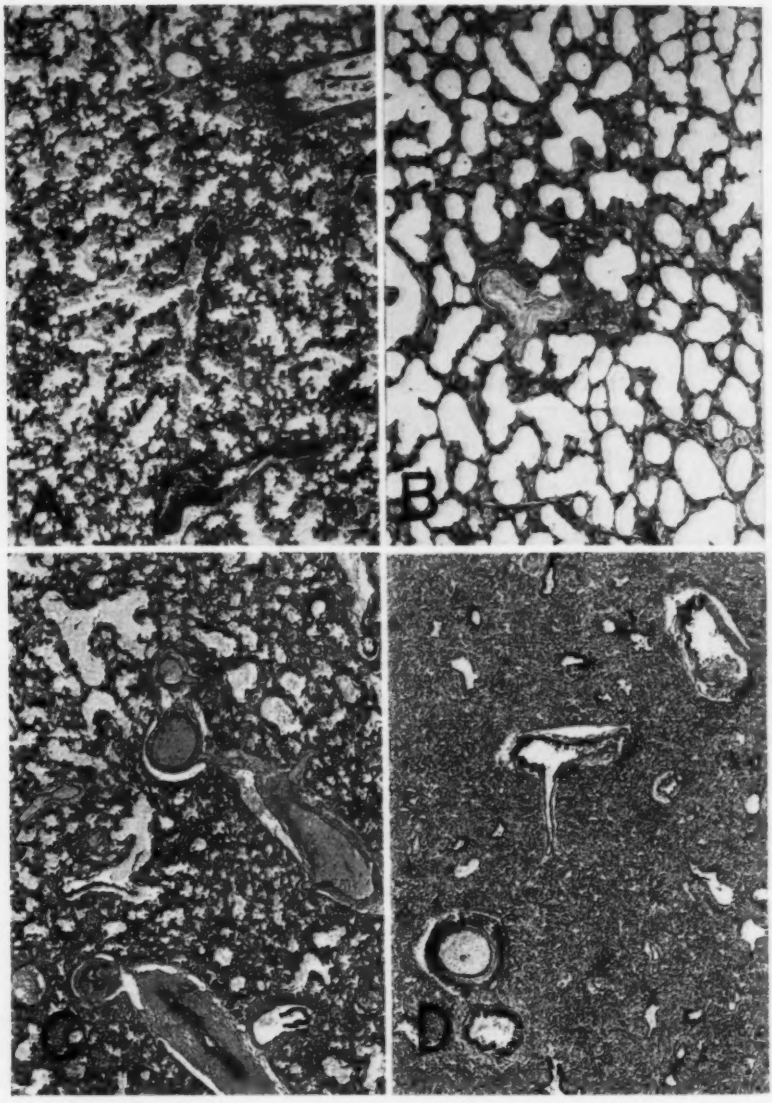

FIGURE 2—Illustrates examples of the method of estimating degree of atelectasis in newborn lungs.

FIG. 2-A. Photomicrograph of a lung of a 2690 gram stillborn female infant delivered of a mother with abruptio placenta. Notice the absence of hyaline membrane and compare the degree of expansion of this lung with B, C, and D. Hematoxylin and eosin (×50).

FIG. 2-B. Photomicrograph of a lung of a 3500 gram male infant delivered of a mother with far advanced active tuberculosis, after a 6 hour labor. At birth, infant was cyanotic

Figure 1-B, 1-C and 1-D which show the variations (Grade I to IV) that exist in the microscopic pictures of the infants dying with hyaline-like membranes. All four cases illustrated in Figure 1 are examples of varying degrees of hyaline-like membranes found in association with atelectasis. The pulmonary pathologic findings in these cases may be considered the primary causes of death.

A system for grading the hyaline-like membranes can be tabulated as follows:

Grade I Scattered, irregular, thin membranes in a few alveolar ducts and alveoli.

Grade II Thin membranes with wide distribution in the alveolar ducts and alveoli.

Grade III Thicker membranes, well distributed in at least 75% of the expanded air ducts and alveoli.

Grade IV Very thick membranes in all expanded alveolar ducts and alveoli.

At first, the above method of grading might appear to be complicated, but with practice it can be used with some degree of quantitative measurement of pulmonary hyaline-like membranes. Three of the authors could independently compare their results and be within 90 per cent agreement. We have continued to apply this grading system in our current survey of perinatal pathology. It should be noted that both Miller and Jennison (13), and Bruns and Shields (6) have used similar methods of grading. A method for estimating the degree of atelectasis in the new born lungs is also necessary. In the past, several different methods have been advocated. They can be itemized as follows:

1. Measurement of thickness of alveolar walls (3).

2. Counting the number of alveoli in one square millimeter. Five different millimeter areas are averaged.

3. The number of epithelial lined bronchioles per low power field of the microscope.

4. The fourth method, namely the estimation of the percentage of area of lung to the area of the alveolar spaces was carried out by the authors of this paper. The method is illustrated in Figure 2 where the photomicrographs

and had difficulty in breathing. Lived 36 hours. Notice the mucous plug in the terminal bronchiole and Grade I membrane. Lung tissue, alveolar space ratio is 20 per cent. Hematoxylin and eosin (×50).

FIG. 2-C. Photomicrograph of a lung of a 1680 gram female infant of a 16 year old mother with severe preeclampsia. No labor. Delivered by cesarean section. Infant poor at birth, 10 minutes of positive pressure resuscitation. Infant lived 41 hours. Grade III membrane with 60 per cent atelectasis. Hematoxylin and eosin (×50).

FIG. 2-D. Photomicrograph of a 1200 gram male infant delivered of a normal mother supposedly at term, after a 4 hour labor. Retraction at birth increased. Infant lived 36 hours. Grade II membrane, associated with 90 per cent atelectasis. Hematoxylin and eosin (×50).

show an increasing percentage of pulmonary atelectasis. On this basis it was possible to study the lungs in the 124 cases with hyaline-like membranes and assign a percentage degree of atelectasis. For example, Figure 2-B is a photomicrograph of the lung of a 3,500 gram male infant delivered of a mother with far advanced tuberculosis after a six hour labor. At birth the infant was cyanotic and had difficulty in breathing. The infant lived for 36 hours. At autopsy, a large amount of mucous was found in the tracheobronchial passages. Microscopic sections of the lungs, Figure 2-B, show distended alveoli as compared to Figure 2-A, the lungs in a stillbirth. Although Grade I hyaline-like membranes are present, the lung tissue to alveolar space percentage is only about 20 per cent. This is an example of the use of grading and estimating the degree of atelectasis. The primary cause of death in this case is not atelectasis. In our classification the case should be listed under anoxia. Compare Figure 2-C and 2-D in which the degree of atelectasis with hyaline-like membranes may be described as a primary cause of death. In the remainder of the paper we shall refer to this condition as "atelectasis with associated hyaline-like membranes" to distinguish this group from those cases of hyaline-like membranes without atelectasis.

In the attempt to discover clinical differences in the deaths in which the lungs showed varying degrees of membranes and atelectasis, our cases were divided into the following five groups:

Group A—283 cases of neonatal deaths in which autopsies were performed without pulmonary hyaline-like membranes comprise a control for the other groups.

Group B—124 neonatal deaths with pulmonary hyaline-like membranes.

Group C—60 cases selected from Group B having only Grade I membranes and less than 70 per cent atelectasis.

TABLE II

Comparison of Mortality of Pulmonary Hyaline-Like Membranes Expressed as Rates per 1000 Live Born Infants in Increments of 500 Grams

Johns Hopkins Hospital

1937–1949

Infant Weight (Grams)	Live Born Infants	Total Neonatal Deaths		Autopsied Neonatal Deaths		Group A		Group B		Group C		Group D		Group E	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
2500+	23458	167	7.1	150	6.4	124	5.3	26	1.1	15	0.6	11	0.47	5	0.21
2000–2499	1928	78	46.7	64	33.2	34	17.6	30	15.5	12	6.2	18	9.3	15	7.8
1500–1999	559	110	196.7	89	159.2	55	98.4	34	60.8	17	30.4	17	30.4	11	19.6
1000–1499	268	125	466.4	104	388.0	70	261.2	34	126.8	16	59.7	18	67.2	11	41.0
Total	26213	480	18.3	407	15.5	283	10.8	124	4.7	60	2.3	64	2.4	42	1.6
Total Prematures (1000–2499 gms.)	2755	313	113.6	257	93.3	159	57.7	98	35.6	45	16.3	53	19.9	37	13.4

Group D—64 cases selected from Group B having Grade II, III, or IV pulmonary hyaline-like membranes with at least 70 per cent atelectasis.

Group E—42 cases selected from Group D in which no other possible cause of death could be ascertained.

In Table II a comparison of the mortality in these various groups is illustrated. Although the frequency (as found at autopsy) of hyaline-like membranes in general is 4.7 per thousand live births, when the membranes are combined with at least 70 per cent atelectasis the incidence per thousand live births falls to 2.4. It must be remembered that this incidence is based on cases with autopsies. There were 73 deaths without autopsy excluded from this study. Assuming the incidence to be the same as in the autopsied cases (30.5 per cent) the total number of cases would be 146 which would increase the incidence of pulmonary hyaline-like membranes to 5.6 per 1,000 live births (over 1,000 grams in weight). In the past literature only a few authors have been careful in the expression of the incidence of this condition in regard to the definition of a live birth and its weight in grams or length in centimeters. A random selection of the previous literature on the incidence of this condition can be tabulated as follows:

Author	Condition	Incidence Per 1000 Live Births
Potter (14, 15)	(Resorption atelectasis with hyaline membrane)	
	Full term	0.6
	Premature	3.0
	Total	3.6
Bruns and Shields (6)	(Pulmonary hyaline membranes)	6.8
Miller and Jennison (13)	(Pulmonary hyaline membranes)	7.8
U. S. Vital Statistics 1950	(Asphyxia and atelectasis)	3.6
Present Study	(Pulmonary hyaline-like membranes)	
	Full term, over 2500 grams	0.99
	Prematures (1000–2499 grams)	3.74
	Total	4.73
	Atelectasis with pulmonary hyaline-like membranes	
	Full term	0.42
	Prematures	2.02
	Total	2.44

The above tabulation would indicate that the reported incidence of pulmonary hyaline-like membranes as found at autopsy is in the range of 4 to 8 per thousand live births as compared to an incidence of 2 to 4 per thousand live births when atelectasis is also present.

At this point a few references to the literature must be introduced. Approximately 40 papers have appeared in the past with 872 cases of pulmonary

TABLE III

Maternal Factors Expressed in Per Cent in the Present Study and Compared to Data from the Literature

Factor	Group A	Group B	Group C	Group D	Group E	Literature
Race: % White	38.1	45.1	36.7	53.0	54.7	62–65
Primigravida	42.7	31.4	33.4	29.6	26.2	—
Private patients	8.8	12.9	6.7	18.7	16.7	—
Rh negative	6.7	4.8	3.3	6.2	2.4	1.6–3.2
Syphilis, history	18.4	13.7	15.0	12.5	9.5	1.6
Abnormal pelvis	25.1	23.5	20.0	26.5	19.0	—
Inadequate prenatal care	32.1	35.5	31.7	39.0	42.8	47
Anemia (under 9 grams)	27.1	16.1	23.4	9.4	9.5	—
Previous death in utero	7.1	9.7	10.0	9.4	11.9	—
Tuberculosis	1.4	0.8	1.6	0.0	0.0	—
Pneumonia	0.7	1.6	1.6	1.6	2.4	—
Diabetes	2.1	3.2	5.0	1.6	2.4	3.1–6.4
Heart disease	3.2	0.8	0.0	1.6	2.4	—
Virus infection	1.4	0.0	0.0	0.0	0.0	—
Toxemia	24.4	18.5	21.7	15.6	19.0	2.9–19.3
Bleeding 1st and 2nd trimester	3.9	5.6	6.7	4.7	4.8	—
Bleeding, third trimester	12.4	16.1	20.0	12.5	11.9	—
Hydramnios	7.1	2.4	1.6	3.1	0.0	—
No maternal complications	67.4	68.5	70.1	67.1	66.7	—

hyaline-like membranes reported. Only a few of the more recent papers have attempted to correlate the maternal clinical histories with the pathologic condition described. Many of the papers do not attempt to report the incidence of the disease because of the random method in the selection of their cases. Only a few studies are from obstetrical services in which proper autopsy percentages are maintained. Many difficulties are therefore encountered in accepting some of the data reported in regard to maternal complications during pregnancy and labor. In Table III the maternal factors expressed as the percentage in each group A to E are compared to the data available in the literature. Approximately 65 to 70 per cent of the patients in Group A as well as the other Groups B to E do not have complications during pregnancy. Analysis of the maternal factors relative to the control Group A as compared to Groups B to E was disappointing. As can be deduced from Table III many factors which are associated with neonatal mortality without the presence of pulmonary hyaline-like membranes were present in the groups (B to E) in equal or less amount expressed in per cent of the total cases in each individual group. Such factors as a history of syphilis, abnormal pelvis, anemia, previous death in utero, inadequate prenatal care, toxemia and vaginal bleeding are frequently associated with prematurity and thereby play an associated role in the etiology of pulmonary hyaline-like membranes.

A comparison of the present study and the previous literature related to

TABLE IV

Comparison of the Present Study and the Previous Literature Related to Complications of Labor and Delivery

Complication	Group A	Group B	Group C	Group D	Group E	Literature
Induction of labor	8.8	6.4	6.7	6.2	9.5	8.2
Intrapartum fever over 100.4°	13.8	8.1	13.4	3.1	0.0	17.7
Premature rupture of membranes (24 or more hrs. before delivery)	12.7	8.9	15.0	3.1	2.4	1.0
Bleeding during labor	12.1	5.6	6.7	4.7	7.1	—
Placenta previa	4.9	10.5	13.4	7.8	4.8	5.7–9.3
Abruptio placenta	4.6	4.0	6.7	1.6	2.4	2.9–5.2
Prolapse of cord	2.5	2.4	3.3	1.6	0.0	0.0–0.7
Maternal shock	4.9	6.4	3.3	9.4	4.8	—
Prolonged labor (over 24 hours)	9.9	3.2	5.0	1.6	0.0	—
Inertia and dystocia	13.8	5.6	6.7	4.7	0.0	5.2
Fetal distress in utero	12.1	8.9	10.0	7.8	4.8	0.0–6.2
Breech delivery	16.9	13.7	8.4	18.7	11.9	9.3–19.3
Internal version and breech extraction	3.2	3.2	5.0	1.6	0.0	2.1–5.7
Cesarean section	8.1	29.1	30.0	28.2	33.3	14.3–16.2
No complication of labor	33.5	41.1	33.4	48.4	59.5	—

TABLE V

Comparison of Various Fetal Factors in the Present Study and the Previous Literature

Factor	Group A	Group B	Group C	Group D	Group E	Literature
Female	35.3	40.3	50.1	31.2	30.9	35.5
Oxygen at birth	54.8	58.8	61.8	56.2	57.1	—
Positive pressure O_2 therapy	13.8	7.3	5.0	9.4	9.5	—
Multiple pregnancy	6.4	8.1	5.0	10.9	7.1	3.2–29.8
Premature under 2500 grams	56.1	79.8	75.2	84.2	88.1	50–100
Pneumonitis	20.8	22.6	31.7	14.1	7.1	20–100.0

the complications of labor and delivery is illustrated in Table IV. Here again the control Group A had approximately the same percentage of complications as Groups B to E. Approximately 35 to 40 per cent of these cases had no complication of labor. However, Groups D and E were slightly higher, 48 to 60 per cent. The most significant point about the delivery was the increase of pulmonary hyaline-like membranes with Cesarean section.

In Table V a comparison was made of the various fetal factors in the present study and in the previous literature. Although there are not great differences between infants dying without pulmonary hyaline-like membranes and those with membranes, it is important to call attention to the increased incidence of prematurity and multiple pregnancy. The administration of oxygen at birth is almost a routine procedure in this clinic so that it is not surprising that 55 to 60 per cent of the neonatal deaths in each group received this method of

therapy. It should be noted, however, that the percentage of cases in which oxygen was administered was not higher in the hyaline-like membrane group than in the control group. The data in Tables III, IV, and V may be more significant if these factors are compared to the expected incidence and summarized as follows:

Complication	Incidence Average of Present Study and Literature	Expected Incidence	Number Times Expected Incidence
	%	%	
Maternal diabetes	3.7	0.2	18.5
Cesarean section	27.	3.3	8.2
Premature infant	81.0	11.7	6.9
Breech delivery	19.0	3.3	5.8
Multiple pregnancy	5.1	1.2	4.3
Toxemia (maternal)	18.3	7.0	2.6

The neonatal deaths in infants of diabetic mothers are of special interest. Table VI shows the infant weights, lengths of life, and cause of neonatal death in relation to maternal age, parity and method of delivery. Despite the small number of cases studied there are several facts shown that are worthy of comment. It can be seen that five of the eleven infants developed hyaline-like membranes (45.4 per cent) as compared with 30.5 per cent in the total neonatal deaths. Four of the infants were term size, a relationship which is contrary to the finding of hyaline-like membrane predominantly among pre-

TABLE VI

Maternal and Fetal Factors in Diabetes

Johns Hopkins Hospital

(1937–1949)

Case No.	Mat. Age	Parity	Type of Delivery	Infant Weight in Grams	Length of Life	Specific Cause of Death	Grade of Hyaline-Like Membrane	Heart Findings
1	33	21011	Spontaneous	3300	Under 6 hours	Abnormal pulmonary ventilation	Grade II	None
2	37	42021	Spontaneous	2015	18 days	Anoxia, diabetes	Grade I	None
3	30	44004	Cesarean section	2500	6 hours	Anoxia, diabetes	Grade I	None
4	34	00000	Spontaneous	2750	20 hours	Anoxia, diabetes	Grade II	None
5	37	55003	Cesarean section	5160	37 hours	Anoxia, diabetes	Grade II	None
6	22	00000	Low forceps	3225	Under 6 hours	Unknown without toxemia	None	None
7	30	87015	Version & extraction	1350	Under 6 hours	Abruptio placenta	None	None
8	37	00000	Breech extraction	4750	Under 6 hours	Anoxia, diabetes	None	Hypertrophy
9	40	32012	Spontaneous	4730	Under 6 hours	Anoxia, diabetes	None	Hypertrophy
10	22	11001	Spontaneous	1625	9 hours	Abnormal pulmonary ventilation	None	None
11	21	00000	Low forceps	2540	22 hours	Multiple anomalies	None	None

matures in the total group. It is interesting to note that 9 of the 11 infants studied died within the first 24 hours, and a major cause of death was identified in only two. The five infants dying with an associated hyaline-like membrane had no additional pathological findings with the exception of anoxia and abnormal pulmonary ventilation. In the total group there were two infants that showed cardiac enlargement by weight and measurement. Miller (13) has emphasized cardiac enlargement in the infants of diabetic mothers and attributes the high neonatal mortality rate to cardiac failure. There seems to be no correlation in our series between maternal age or parity in diabetic mothers with the production of hyaline-like membranes in the infant's lungs. Winter and Gellis (17) and other investigators however, have noted an increased incidence in the production of hyaline-like membranes in infants delivered by Cesarean section. Both infants delivered in this manner in the present series demonstrated the lesion while only three of nine infants delivered per vaginum had it.

In an effort to uncover the possibility of clinical errors in the management of mother or infant, further detailed investigations were made. In Table VII the distribution of the various Groups A to E by 500 gram weight increments demonstrated that Group D (Grade II, III, and IV hyaline-like membrane with at least 70 per cent atelectasis) had only two infants over 3,000 grams in weight. In group E there were no infants over 3,000 grams in weight. This

TABLE VII

Distribution and Comparison of Neonatal Deaths Associated with Varying Degrees of Atelectasis and Hyaline-Like Membranes (Groups A to E)

Johns Hopkins Hospital

1937–1949

Infant Weight (Grams)	Group A		Group B		Group C		Group D		Group E	
	No.	%	No.	%	No.	%	No.	%	No.	%
5000 +	2	0.7	1	0.8	1	1.6	0	0	0	0
4500–4999	2	0.7	0	0.0	0	0.0	0	0	0	0
4000–4499	8	2.8	1	0.8	1	1.6	0	0	0	0
3500–3999	34	12.1	4	3.2	3	5.0	1	1.6	0	0
3000–3499	47	16.6	5	4.0	4	6.7	1	1.6	0	0
2500–2999	31	10.9	15	12.2	6	10.0	9	14.1	5	11.9
2000–2499	34	12.1	30	24.2	12	20.0	18	28.1	15	35.7
1500–1999	55	19.4	34	27.4	17	28.4	17	26.5	11	26.2
1000–1499	70	24.7	34	27.4	16	26.7	18	28.1	11	26.2
Total Deaths	283	100.0	124	100.0	60	100.0	64	100.0	42	100.0
Total Term	124	43.8	26	20.9	15	25.0	11	17.2	5	11.9
Total Prematures	159	56.2	98	79.1	45	75.0	53	82.8	37	88.1

TABLE VIII

Relationship of Gestational Age and Various Degrees of Atelectasis and Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

(1937–1949)

Gestational Age (Days)	Group A	Group B	Group C	Group D	Group E
Unknown	1.1	0.8	1.6	0.0	0.0
180–199	9.2	10.5	10.0	10.9	11.9
200–219	13.1	20.9	18.4	23.4	21.4
220–239	15.6	21.8	20.0	23.4	26.2
240–259	13.4	23.5	25.1	21.8	21.4
260–279	20.5	11.3	13.4	9.4	11.9
280–289	16.2	4.8	5.0	4.7	2.4
290–294	4.2	0.0	0.0	0.0	0.0
295–299	2.5	0.8	0.0	1.6	2.4
300–304	2.1	1.6	1.6	1.6	0.0
305–309	0.4	0.8	1.6	0.0	0.0
310 and over	1.7	3.2	3.3	3.2	2.4
Total	100.0	100.0	100.0	100.0	100.0
Over 280	21.8	11.3	11.6	10.9	7.1
Over 295	5.4	6.4	6.7	6.2	4.8

TABLE IX

Type of Delivery in Neonatal Deaths Associated with and without Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

Type of Delivery	Group A %	Group B %	Group C %	Group D %	Group E %
Spontaneous with episiotomy	6.4	4.0	3.3	4.7	2.4
Spontaneous without episiotomy	38.5	36.3	35.0	37.5	40.5
Elective low forceps	12.0	6.4	6.7	6.2	7.1
Indicated low forceps	12.4	7.3	11.6	3.1	4.8
Mid forceps	1.7	0.0	0.0	0.0	0.0
High forceps	0.0	0.0	0.0	0.0	0.0
Destructive	0.4	0.0	0.0	0.0	0.0
Cesarean section	8.1	29.1	30.0	28.2	33.3
Breech delivery	20.1	16.9	13.4	20.3	11.9
Unknown	0.4	0.0	0.0	0.0	0.0
Total	100.0	100.0	100.0	100.0	100.0

reemphasizes the fact that the tendency for the more severe degrees of atelectasis associated with hyaline-like membranes is closely allied with the premature infant. Based on this interesting finding the length of gestation of neonatal deaths was analyzed as in Table VIII. A decrease in neonatal deaths

with hyaline membranes over 280 days gestation (11.3 per cent as compared to neonatal deaths without membranes—21.8 per cent) could be demonstrated. This also tends to support the significance of prematurity.

The method of delivery is listed in Table IX. The most significant finding was the increase in births by Cesarean section in all groups with hyaline membranes B to E over the group of neonatal deaths without membranes. Breech delivery is increased over the normal clinic incidence but 23 of the 26 breech deliveries were in premature infants and that finding precludes attaching any significance to this type of delivery.

The incidence of Cesarean section has been described by previous authors as greatly increased and in this series there were 36 such deliveries or 29 per cent of the 124 cases. Pulmonary hyaline membranes occurring in infants delivered by Cesarean section in this study can be tabulated by 500 gram weight groups as follows:

Birth Weight (grams)	Cases	% of Total Cases
2500 +	12	33.3
2000–2499	5	13.9
1500–1999	9	25.0
1000–1499	10	27.8
Total	36	100.0

From the above tabulation, one-third of the Cesarean section cases were in term infants and this represents 46 per cent of all term infants in the present series of 124 neonatal deaths with hyaline membranes. Therefore, as noted in previous papers, (8) Cesarean section appears to play some important etiologic role. In a study of perinatal mortality associated with Cesarean section in the Johns Hopkins Hospital during a ten year period (1941–1950) there were 519 Cesarean sections done under ideal conditions in which the fetal heart was audible, with membranes intact, and no labor or hemorrhagic conditions such as abruptio and placenta previa present in the mother. In these 519 infants (over 2,500 grams) eight neonatal deaths occurred. Every one of the eight infant deaths had some degree of atelectasis associated with pulmonary hyaline-like membranes.

The maternal indications for the Cesarean section in the 12 term neonatal deaths in the present study with hyaline-like membranes was as follows:

Previous Cesarean section ..... 3 Cases
Contracted pelvis ..... 3 Cases
Diabetes ..... 2 Cases
Uterine intertia ..... 2 Cases
Toxemia of pregnancy ..... 1 Case
Intrapartum infection ..... 1 Case

The primary pathologic causes of death in the twelve infants was listed as follows:

Atelectasis with hyaline-like membranes	4 Cases
Maternal diabetes	2 Cases
Infection, pneumonia	2 Cases
Anoxia, abnormal uterine contractions	1 Case
Anoxia, intrapartum fever	1 Case
Anoxia, unknown origin	1 Case
Congenital malformation, heart	1 Case
	12 Cases

There were 16 term Cesarean neonatal deaths in the entire study of 407 cases and 12 infants or 74.5 per cent had atelectasis and associated pulmonary hyaline-like membranes. These data would support the previous literature that factors surrounding Cesarean section play a large role in the etiology of this condition.

The role of analgesia and anesthesia is tabulated in Tables X and XI. In general, less analgesia was used in Groups D and E than in the control Group A. Since the number of premature infants is greater in Groups D and E and as the clinic policy has been to use less analgesia in premature labor, this point becomes less significant. As shown in Table X there was a slight increase in the use of intravenous anesthesia in Groups D and E over the control Group A.

The condition at birth of neonatal deaths with and without pulmonary hyaline-like membranes associated with various degrees of atelectasis (Groups A to E) is shown in Table XII. It must be pointed out that it is very difficult to deal with descriptive terminology of the newborn in the first few hours of

TABLE X

Maternal Anesthesia Associated with Neonatal Deaths

Johns Hopkins Hospital

(1937–1949)

Anesthesia	Group A %	Group B %	Group C %	Group D %	Group E %
No anesthesia	23.7	19.3	20.0	18.7	16.7
Inhalation	47.3	46.8	53.3	40.7	47.6
Intravenous	10.9	12.1	6.7	17.2	14.3
Conduction: epidural	0.7	0.0	0.0	0.0	0.0
Conduction: caudal	6.4	4.0	5.0	3.1	0.0
Conduction: saddle block	3.2	2.4	3.3	1.6	0.0
Conduction: spinal	4.2	0.8	1.7	0.0	0.0
Local	1.4	4.8	3.3	6.2	7.1
Combined	2.2	9.8	6.7	12.5	14.3
Total	100.0	100.0	100.0	100.0	100.0

TABLE XI

Maternal Analgesia Associated with Neonatal Deaths

Johns Hopkins Hospital

1937–1949

Analgesia	Group A %	Group B %	Group C %	Group D %	Group E %
Barbiturates	25.1	12.1	16.7	7.8	11.9
Morphine, or substitute	13.4	7.3	13.4	1.6	2.4
Paraldehyde	2.5	1.6	1.6	1.6	0.0
Amnesics	0.4	1.6	1.6	1.6	0.0
Conduction	5.6	7.3	5.0	9.4	2.4
Inhalation	0.0	0.8	0.0	1.6	2.4
Other	1.1	2.4	1.6	3.1	4.8
None and psycho-analgesia	51.9	66.9	60.1	73.3	76.1
Total	100.0	100.0	100.0	100.0	100.0

TABLE XII

Condition at Birth of Neonatal Deaths with and without Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

Condition	Group A %	Group B %	Group C %	Group D %	Group E %
Excellent	18.4	19.3	16.7	21.8	26.2
Fair, poor respiration, good heart	31.4	44.4	43.4	45.3	35.7
Poor, apneic, fair heart	33.2	33.1	38.4	28.2	30.9
Poor, apneic, irregular heart	14.8	2.4	1.6	3.1	4.8
Poor, fair respirations, poor heart	1.1	0.8	0.0	1.6	2.4
Unknown	1.1	0.0	0.0	0.0	0.0
Total	100.0	100.0	100.0	100.0	100.0

life. In the past, most authors have reported the presence of spontaneous respiration in the first few minutes of life. (11, 12, 13, 16) As seen in Table XII, about 60 per cent of the infants with atelectasis and hyaline membranes (Groups D and B) are in fair to excellent condition at birth. Following birth, however, a wide range of symptoms are described including dyspnea, cyanosis, retraction, and apnea. In recent years the breathing pattern of infants with this condition is said to be characteristic in that very little abdominal or diaphragmatic participation is seen in contrast to the normal newborn in which both chest and abdominal breathing is observed. Closer observation at the time of birth on a large series of infants will be necessary before final conclusions can be reached.

The length of life or survival time averages about 30 hours. In Table XIII some interesting comparisons in survival time of infants with and without

TABLE XIII

Survival Time of 124 Infants with Various Degrees of Atelectasis and Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

Survival Time	Group A %	Group B %	Group C %	Group D %	Group E %
Under 6 hours	26.2	12.1	15.0	9.4	4.8
6–11 hours	9.5	23.5	20.0	26.5	33.3
12–17 hours	9.5	14.4	15.0	14.1	16.7
18–23 hours	4.6	12.1	10.0	14.1	11.9
First day	49.8	62.1	60.0	64.1	66.7
Second day	12.4	24.2	20.0	28.1	30.9
Third day	10.2	8.9	11.6	6.2	2.4
4–6 days	13.4	1.6	1.7	1.6	0.0
7–14 days	7.8	1.6	3.3	0.0	0.0
15–21 days	3.9	0.8	1.7	0.0	0.0
22–30 days	2.1	0.8	1.7	0.0	0.0
Unknown	0.4				
Total	100.0	100.0	100.0	100.0	100.0

pulmonary hyaline-like membranes are recorded. Group A tends to substantiate the well known data that 50 per cent of neonatal deaths occur in the first twenty-four hours of life. Although some infants with hyaline membranes (Group B) can be seen throughout the first 30 days of life, it should be noticed that all infants in Group D and E are dead in 3 days (Group E) to 6 days (Group D).

In an attempt to correlate the survival time of infants with varying grades of pulmonary hyaline-like membranes, Table XIV was prepared. The data suggest that the higher the grade, the shorter the survival period. This fact would tend to support the idea that the hyaline material itself can be an important factor in producing the death of the infant.

Another interesting point in this study was the association of pulmonary hyaline-like membranes with various degrees of an inflammatory reaction. It must be remembered that the entire subject of hyaline-like membranes in newborn lungs was introduced in the literature as a type of pneumonia. Among the 124 cases in the present study there were 29 infant lungs that had some inflammatory changes, such as leukocytic infiltration of the alveoli or alveolar walls in addition to various grades of hyaline membranes and atelectasis. The distribution of these 29 infants with pulmonary infection and of the 95 infants without pulmonary infection was correlated with their survival time as illustrated in Table XV. This table demonstrates that infants with pulmonary hyaline-like membranes associated with pneumonitis lived a little

TABLE XIV

Survival Time of 124 Infants with Grades I to IV Pulmonary Hyaline-Like Membranes

John Hopkins Hospital

1937–1949

Survival Time	Grade I		Grade II		Grade III		Grade IV		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Under 6 hours	5	13.5	9	16.7	0	0	1	20.0	15	12.1
6–11 hours	3	8.1	22	40.8	4	14.3	0	0	29	23.4
12–17 hours	6	16.2	7	12.9	5	17.8	0	0	18	14.5
18–23 hours	3	8.1	7	12.9	4	14.3	1	20	15	12.1
First day	17	45.9	45	83.3	13	46.4	2	40.	77	62.1
Second day	10	27.1	6	11.2	11	39.3	3	60.	30	24.5
Third day	5	13.5	2	3.7	4	14.3	0	0	11	8.8
4–6 days	1	2.7	1	1.8	0	0	0	0	2	1.5
7–14 days	2	5.4	0	0.0	0	0	0	0	2	1.5
15–21 days	1	2.7	0	0.0	0	0	0	0	1	0.8
22–30 days	1	2.7	0	0.0	0	0	0	0	1	0.8
Total	37	100.0	54	100.0	28	100.0	5	100.0	124	100.0

TABLE XV

Distribution of Infants with Pulmonary Hyaline-Like Membranes with and Without Infection Correlated with Survival Time

Survival Time (hours or days)	29 Infants with Pulmonary Infection %	95 Infants without Pulmonary Infection %
Less than 6 hours	6.8	13.7
6–11 hours	10.3	27.4
12–17 hours	17.2	13.7
18–23 hours	10.3	12.6
First day	44.6	67.4
Second day	24.2	24.2
Third day	24.2	4.2
4–6 days	0.0	2.1
7–14 days	3.5	1.0
15–21 days	0.0	1.0
22–30 days	3.5	0.0
Total	100.0	100.0

longer than those without pulmonary infection. Potter (15) maintains that infants with hyaline membranes who live longer than 48 hours tend to develop pneumonitis.

In an effort to determine whether the duration of ruptured membranes in the mother had any relation to the pulmonary infection present in some in-

TABLE XVI

The Duration of Ruptured Membranes in the Mother and Pulmonary Infection in Infants with Hyaline-Like Membrane

Duration Ruptured Membranes (hours before delivery)	29 Infants with Pulmonary Infection %	95 Infants without Pulmonary Infection %
Not ruptured	37.9	43.2
Less than 6	24.2	36.8
6–11	13.7	8.4
12–17	6.9	0.0
18–23	3.5	4.2
First day	86.2	92.6
Second day	0.0	5.3
3–4 days	6.9	1.0
5–7 days	3.5	1.0
8–10 days	0.0	0.0
Over 10 days	3.5	0.0
Total	100.0	100.0

TABLE XVII

Cases of Hyaline-Like Membrane Associated with Pulmonary Infection and Maternal Intrapartum Fever

Degree of Maternal Intrapartum Fever	Pulmonary Infection		No Pulmonary Infection	
	Cases	Per Cent	Cases	Per Cent
None (less than 100.4°)	24	82.8	89	93.7
Fever from 100.4° to 102°	4	13.7	4	4.2
Fever from 102° to 104°	1	3.5	2	2.1
Fever over 104° F.	0	—	0	—
Totals	29	100.0	95	100.0

fants with hyaline-like membranes, Table XVI was prepared. Apparently 24 hours of ruptured membranes made little difference; however some appreciable differences were observed with ruptured membranes of 3 to 4 days or longer. In Table XVII the 29 cases of pulmonary hyaline-like membranes associated with pneumonitis were compared to the 95 cases without pneumonitis and the degree of maternal intrapartum fever. As was to be expected, there was a distinct increase of pulmonary infection in the newborn lung in those cases in which the maternal temperature was over 100.4°F. during labor.

As we have already pointed out, hyaline membranes are found associated with other clinical and pathological conditions. Therefore, the presence of hyaline membranes with or without atelectasis cannot always be the primary cause of death. The early reports in the literature were often prepared without a strict primary classification of the causes of perinatal deaths. It is possible

that maternal complications could be eliminated as etiologic if the classification listed below were not used.

I. Anoxia
  Placenta
  Cord
  Maternal complications
  Complications of labor
  Other
II. No abnormal state
  Without maternal disease
  With toxemia
  Other acute or chronic disease
  Maternal diabetes
III. Birth injury
IV. Malformation
V. Abnormal pulmonary ventilation
VI. Infection
  Syphilis
  Other infection
VII. Erythroblastosis
VIII. Other conditions or causes
IX. Therapeutic interference (under 1000 grams)

In the above listing, atelectasis, associated with hyaline-like membranes, when sufficient to meet the criteria set up by the authors as a cause of death, would be placed under the broad term of "Abnormal Pulmonary Ventilation." It should be pointed out that it is not always easy to decide which of the above nine headings to use as the primary classification of death. In an effort to illustrate these difficulties, four representative cases have been selected and photomicrographs of the lungs have been prepared.

CASES ILLUSTRATING THE DIFFICULTIES OF CLASSIFICATION

Case 1. History No. 194458.

The mother of this infant was a 30 year old white, married, para 4-0-0-2, who was Rh negative with antibodies. Her clinical pelvic measurements were normal. Labor was induced at 39 weeks by artificial rupture of membranes. After a labor of four hours, a 3,030 gram male infant which cried spontaneously was delivered under caudal anesthesia. The infant was jaundiced and a diagnosis of erythroblastosis was made. Exchange transfusion was performed, but the infant died after two hours of life. At autopsy, the characteristic findings of erythroblastosis were present; hepatomegaly, splenomegaly and diffuse extramedullary blood formation in all viscera and the placenta. However, the lungs demonstrated Grade III hyaline membranes with 60 per cent atelectasis, (Fig. 3-A).

In spite of the pulmonary findings, the primary cause of death was coded as "Erythroblastosis".

Case 2. History No. 348389.

The mother of this infant was a 37 year old white, para 5-0-0-3, with diabetes of two years duration. Her last two infants were stillbirths, the last one necessitating decapitation due to excessive size. During the thirty-seventh week of the present pregnancy the patient entered the hospital with severe preeclampsia. Rupture of membranes was performed, but labor did not ensue. Classical cesarean section was performed under sodium pentothal (10 minutes before delivery) anesthesia. A 5,160 gram male infant, whose breathing and crying time were immediate, was delivered without difficulty. Cyanosis and edema were noted a few hours after delivery and respirations became labored and increasingly difficult with marked retraction of the ribs. The infant died after 37 hours of life and in Figure 3-B a photomicrograph of its lungs shows a Grade II membrane and 65 per cent atelectasis.

In spite of the presence of hyaline-like membranes in the lungs the numerous physio-

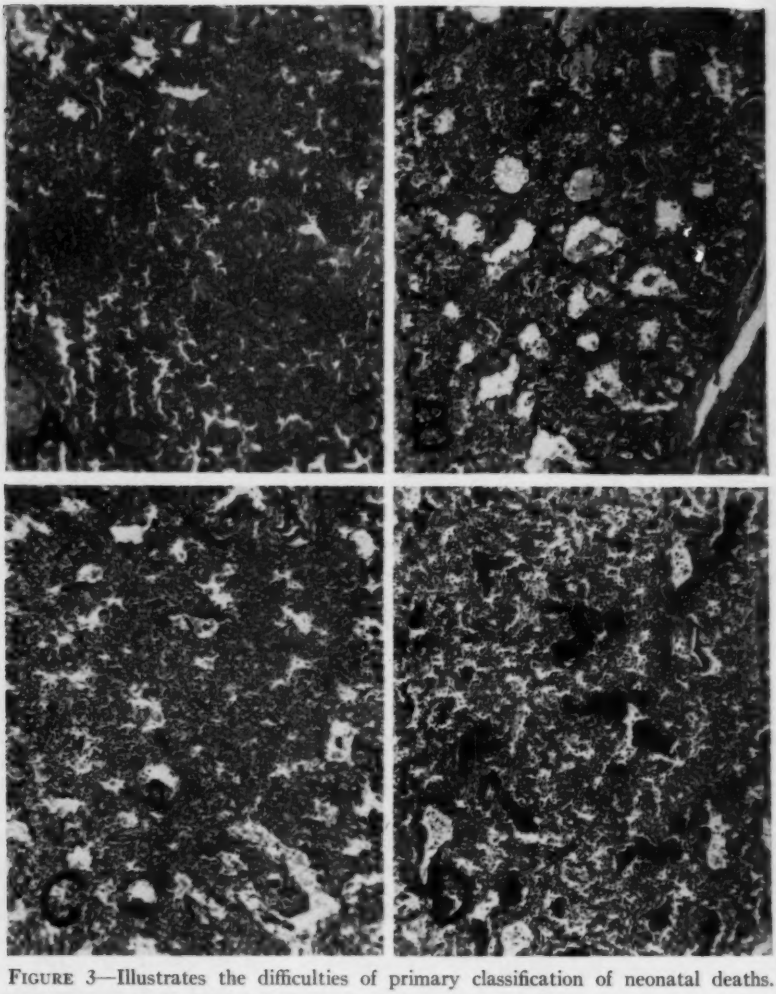

FIGURE 3—Illustrates the difficulties of primary classification of neonatal deaths.

FIG. 3-A. Photomicrograph of a lung of a 3030 gram male infant delivered spontaneously after a 4 hour labor of an Rh negative multipara, with antibodies. Cried spontaneously, received exchange transfusion, died after 2 hours of life. Note Grade III hyaline like membrane with 60 per cent atelectasis. This death was given primary classification of erythroblastosis. Hematoxylin and eosin (×100).

FIG. 3-B. Photomicrograph of a lung of a 5160 gram male infant of a 37 year old diabetic multipara by cesarean section in 37th week of gestation. Anesthesia, sodium pentothal 10 minutes before delivery. Breathing and crying time immediate, but cyanosis shortly after. Lived 37 hours. Grade III membrane and 65 per cent atelectasis. Given primary death classification of, No abnormal state—diabetes. Hematoxylin and eosin (×100).

FIG. 3-C. Photomicrograph of a lung of a 1780 gram male infant delivered by cesarean

pathologic alterations of the diabetic infant such as anoxia, heart failure and chemical difficulties make the primary classification of death in this condition difficult. Arbitrarily we placed this under the primary cause of death in our classification as "No Abnormal State: With Maternal Diabetes". The reader may not agree.

Case 3. History No. 510914.

The mother of this infant was 22 year old Negro, married, unregistered, para 2-0-0-2, blood type O Rh positive and serologically negative for syphilis. Her previous pregnancies had been uneventful. In the thirty-second week of the present pregnancy the patient developed painless vaginal bleeding. No signs or symptoms of shock were present. A sterile vaginal examination did not reveal placenta previa; hence the diagnosis was thought to be abruptio placenta. A low cervical Cesarean section was performed under sodium pentothal anesthesia. The anesthetic was administered for 12 minutes prior to the delivery of a 1,780 gram male infant. It breathed immediately but did not cry for 12 minutes. The infant's general condition was only fair since a period of apnea followed its initial breathing and required the use of positive pressure oxygen and artificial resuscitation. The infant was cyanotic with noisy respiration and costal rib retraction. Edema of the hands and feet with increasing respiratory difficulties developed and finally the infant became spastic and died after 40 hours of life. Examination of the placenta showed complete circumvallation and a form of abruptio due to rupture of the marginal sinus. An autopsy of the infant revealed scattered petechiae over the pericardium and pleura, renal hemorrhages, and Grade III pulmonary hyaline-like membranes, with 80 per cent atelectasis of the lungs (Fig. 3-C).

This case was coded as a primary cause of death under "Anoxia due to Abruptio Placenta". There may be many readers who will object, but the case proves the point as to why so many reports have no maternal complications listed as being associated with atelectasis with pulmonary hyaline-like membranes.

Case 4. History No. 102490.

The mother of this infant was a 38 year old Negro, para 4-0-0-4, who was Rh positive and serological tests for syphilis were negative. During the pregnancy some antepartum bleeding had occurred in the eighth week. At the time of labor the blood pressure of the mother was 140/90 mm. of mercury. After 21 hours of labor a 2,480 gram male infant was delivered as a face presentation spontaneously. The infant breathed immediately, but did not cry and persistent cyanosis was present. Oxygen with positive pressure was administered, but the infant lived only 30 hours. At autopsy massive bilateral ventricular and subarachnoid hemorrhages were present. As illustrated in Figure 3-D, the lungs showed about 70 per cent atelectasis and a Grade IV membrane.

In previous years this death was coded as a "Birth Injury". In recent years the type of brain hemorrhage, namely intraventricular and subarachnoid would be interpreted by many as due to "Anoxia." In any event the clinical and pathologic findings associated with

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section of a mother with abruptio placenta. Infant in fair condition at birth followed by period of apnea, requiring resuscitation. Lived for 40 hours. Although lung shows Grade III membrane with 80 per cent atelectasis the primary cause of death was coded as anoxia, due to abruptio. Hematoxylin and eosin (×100).

FIG. 3-D. Photomicrograph of a lung of a 2480 gram male infant delivered of a 38 year old multipara with mild preeclampsia after a 21 hour labor. Persistent cyanosis at birth, infant lived for 30 hours. Massive bilateral ventricular and subarachnoid hemorrhage at autopsy. Lungs show Grade IV membrane, and 70 per cent atelectasis. This death was coded as a birth injury. In recent years such cases probably have been coded under anoxia. Hematoxylin and eosin (×100).

TABLE XVIII

Comparison of Primary Cause of Neonatal Deaths and Associated Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

Cause of Death	Autopsied Neonatal Deaths	Deaths with Hyaline Membranes	% Neonatal Deaths
Anoxia	85	24	28.2
No abnormal state	58	19	32.8
Birth injury	76	19	25.0
Malformation	53	6	11.3
Abnormal pulmonary ventilation	73	38	52.1
Infection	44	12	27.3
Erythroblastosis	11	2	18.2
Other conditions or causes	7	4	57.1
Total	407	124	30.5

the infant's lungs are not to be ignored, and it is possible that many authors would categorize this case as "Abnormal Pulmonary Ventilation".

These four cases are examples of the difficulties encountered in classification of neonatal deaths under one primary cause. If we attempt to group our cases of pulmonary hyaline-like membranes with other causes of death that we have used through the years in primary classification of perinatal mortality, the grouping would be as illustrated in Table XVIII. An effort was made to portray the major causes of neonatal death associated with various degrees of hyaline-like membranes and also the percentage of atelectasis as determined by the method described earlier in this study, Table XIX. This table shows it is very difficult to be absolutely certain in many instances which cause of death should be designated as the primary one, and whether or not to consider atelectasis and hyaline membrane as an associated cause of death. Table XIX demonstrates how important it is to have a reliable classification of neonatal deaths in the obstetric and pediatric services from which studies on atelectasis and associated hyaline membranes are reported. The classification depends upon evaluation of the total factors involved in each case so as to establish the specific cause of death. This table shows that many cases with advanced degrees of atelectasis and hyaline-like membrane actually died from other causes or in association with other major pathologic findings. The fact that cases with hyaline-like pulmonary membranes are found in all major categories of neonatal death is shown even more dramatically in Table XVIII. There is, therefore, little doubt that the mere presence of a hyaline-like membrane does not preclude other important pathologic factors that influence neonatal deaths. We have found hyaline-like membrane cases associated with anoxia, birth injury, malformation, infection, erythroblastosis, maternal diabetes and prematurity. In general, there are at least three different groups of cases with

TABLE XIX

Comparison of the Primary Cause of Death Associated with Atelectasis and Pulmonary Hyaline-Like Membranes

Johns Hopkins Hospital

1937–1949

	Cause of Death	Group A	Group B	Group C	Group D	Group E	Literature
I	Anoxia	19.1	25.0	31.7	18.7	16.7	
	Placenta previa	3.9	7.3	8.4	6.2	4.8	5.7–9.3
	Abruptio	2.8	4.0	5.0	3.1	4.8	2.9–5.2
	Cord	2.5	0.8	1.6	0.0	0.0	0–0.7
	Maternal complications	1.4	4.0	8.4	0.0	0.0	
	Complications of labor	4.6	2.4	1.6	3.1	0.0	5.2
	Other	3.9	6.4	6.7	6.2	7.1	
II	No abnormal state	16.6	8.9	8.4	9.4	11.9	
	Without maternal disease	11.6	2.4	1.6	3.1	4.8	
	With toxemia	2.8	3.2	1.6	4.7	7.1	
	Other acute or chronic disease	1.1	0.0	0.0	0.0	0.0	
	Maternal diabetes	1.1	3.2	5.2	1.6	0.0	3.1–6.4
III	Birth injury	20.1	15.3	21.7	9.4	0.0	5.7–15.5
IV	Malformation	16.6	4.8	6.7	3.1	2.4	3.2–5.7
V	Abnormal pulmonary ventilation	12.4	30.6	18.4	42.1	64.3	
VI	Infection	10.9	10.5	11.6	9.4	0.0	
	Syphilis	1.7	0.0	0.0	0.0	0.0	
	Other infection	9.2	10.5	11.6	9.4	0.0	
VII	Erythroblastosis	3.2	1.6	0.0	3.1	0.0	
VIII	Other conditions or causes	1.1	3.2	1.6	4.7	4.8	
	Total	100.0	100.0	100.0	100.0	100.0	

pulmonary hyaline-like membranes. First, the neonatal deaths in which the pulmonary hyaline-like membranes are discovered as an incidental finding in the lungs delivered in association with a maternal complication such as intrauterine anoxia or dystocia. Here the autopsy reveals additional pathologic findings and the classification is made accordingly. The second group of cases is noted in autopsies of infants in which the lungs not only have hyaline-like membranes, but are also associated with various degrees of atelectasis. However, in this group numerous clinical and pathological findings are also present which might place the primary classification of the death under such headings as anoxia, birth injury or malformation. The third and final group are easier to classify, since by exclusion no remarkable pathologic findings are present except atelectasis of at least 70 per cent. This type of case is usually present in the term infant delivered by Cesarean section and the premature infant (1,000–2,499 grams) in the mother without known complications.

Since the main purpose of this report was primarily a clinical pathological investigation an extensive discussion of treatment will not be pursued. This study does not answer many questions the reader may have about the origin

of pulmonary hyaline-like membranes. The problem of atelectasis with hyaline-like membranes has reached the stage in knowledge beyond simple morphologic structure visible to the light microscope. Like so many disease problems today its solution may have to be aided by more intimate biophysical, chemical, and metabolic studies. Special investigations on the maternal fetal oxygen exchange under numerous obstetrical situations during pregnancy and labor as well as intensive studies of fetal circulation and capillary permeability may offer leads in this difficult problem of newborn life.

SUMMARY AND CONCLUSIONS

A pathological study of the lungs of 407 infants weighing over 1,000 grams is reported. Of the 407 cases studied histologically 124 or 30.5 per cent were found to have pulmonary hyaline-like membranes. A further analysis reveals an incidence of this lesion per 1,000 live births of 3.7 in the 1,000 to 2,499 gram group and 0.99 in the 2,500 gram and over group. Live born infants between 400 to 999 grams were deleted from the general investigation to achieve biostatistical accuracy. However, in a study of these infants [over a three year period,] thirteen of 52 total immature deaths demonstrated hyaline-like membranes (25 per cent). In the literature there has been some doubt expressed as to whether the lesser weight infants have this entity. The general opinion that hyaline-like membranes are not found in the lungs of stillborn infants was supported by this study in which no single case was discovered in the examination of the lungs of 563 stillbirths.

The hyaline-like membranes were graded I to IV according to thickness and distribution. The degree of atelectasis was estimated in per cent by comparing the areas of lung tissue to the area of alveolar spaces. The cases were further subdivided into 5 groups (A through E) according to the grade of hyaline-like membrane and the percentage of atelectasis. The total incidence of hyaline-like membrane is 4.7 per thousand live births (over 1,000 grams) without significant atelectasis, but when combined with at least 70 per cent atelectasis the incidence of cases falls to 2.4.

Clinical evaluation revealed that the cases of hyaline-like membrane were associated with multiple factors that have a higher incidence than is found in the general clinic average. These factors included prematurity (6.9 times higher) multiple pregnancy, and delivery by Cesarean section (27 per cent of total cases).

There is an increased incidence of hyaline-like membranes also in the lungs of infants of diabetic mothers. This is particularly true in those delivered by Cesarean section. No attempt was made to review the entire literature on this subject except when pertinent to the incidence of various maternal and fetal factors. Almost 900 cases of neonatal death associated with pulmonary hyaline-like membranes have been reported. This study is the largest series with complete clinical information reported in the literature up to the present time.

The infants with pulmonary hyaline-like membranes lived an average of 30 hours, but a definite inverse proportion between length of life and extent of membrane was found. The infants surviving longest usually had less extensive hyaline-like membranes than those infants dying more quickly; and also were found to have a higher incidence of associated pneumonitis. Pneumonitis was found in the lungs of infants most often where there were maternal complications of intrapartum fever and rupture membranes for 3 to 4 days prior to delivery.

The cases in which we considered hyaline-like membranes as the sole cause of death, were in association with 70 or more per cent pulmonary atelectasis. These cases represented nearly 30 per cent of the total hyaline-like membrane group, but only 8.6 per cent of the entire group of neonatal deaths. We believe however that hyaline-like membrane in conjunction with other pulmonary pathology makes up a large group of cases with "abnormal pulmonary ventilation" which ranks high as a causative factor in neonatal death, particularly in the premature group. It should be mentioned however that the presence of major pathologic changes outside the lung confuses the problem of classification and necessitates a very careful clinical and pathologic appraisal of the factors involved. The utilization of a specific pathologic classification that takes into consideration the clinical aspects of each case is a prerequisite to proper assessment.

Any evaluation of the hyaline-like membrane problem must include the degree of associated atelectasis. We believe that atelectasis plays an important role in the physiopathologic evaluation, and it must be considered as well as infection, aspiration phenomena, and other pulmonary changes in expressing the total cases of "abnormal pulmonary ventilation." Since the feature of atelectasis has been seldom experimentally produced we believe the condition of hyaline-like membrane in experimental animals is not totally analogous to the human.

That the problem of hyaline-like membrane in the infant lung is a great one is attested by the fact that approximately one out of every four neonatal deaths in our series had the membrane to some degree. The problem goes hand in hand with prematurity, and it has been suggested that both have common etiologic backgrounds. The problem can be solved only through the application of histochemical, uterine and respiratory physiologic technics. For the present however, the understanding of the relative importance of any given cases of hyaline-like membrane lies in the meticulous assessment of the clinical and pathologic factors.

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DESENSITIZATION OF THE GUINEA PIG TO FORSSMAN ANTIBODY

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The existence of cross-reacting immunologic systems, sometimes known as heterologous or heterophilic phenomena, was known for a number of years (1) when, in 1911, Forssman (2) first described that system which now bears his name. Forssman (2) demonstrated that suspensions of various organs of the guinea pig when injected into rabbits stimulate the production of antibodies which can hemolyze sheep erythrocytes. Of the organs Forssman used, interest has centered on the guinea pig kidney, but it has since been found that other animal tissues and many bacteria will incite the production of sheep hemolysins when injected into rabbits. Thus, this property is shared by tissues of the guinea pig, horse, dog, cat, chicken and mouse, by the pneumococcus, Shigella shigae and various other bacteria (1, 3, 4), and by sheep erythrocytes. It is believed that this common property is attributable in many instances to the presence of the so-called Forssman antigen, and when such is the case the antibody formed thereto (i.e., the hemolysin) is generally known as the Forssman antibody. In the strictest sense, the Forssman antibody is defined as any antibody which will, on the one hand, hemolyze sheep erythrocytes, but, in addition, will be absorbed *in vitro* by guinea pig kidney. The Forssman antibody can be produced in response to the injection of Forssman antigen only by those animals which do not contain Forssman antigen (3), of which the rabbit is the prototype.

Although it is well known that the Forssman antigen is a heat-stable, alcohol soluble substance (1, 4), and although it is often stated that it is a hapten, probably a lipopolysaccharide (3, 4), the precise chemical nature of the Forssman antigen is controversial and unknown.

While it is quite logical that the sera of rabbits immunized with Forssman antigen will contain Forssman antibody, it is a well known but poorly understood fact that the sera of most normal rabbits and even some humans contain small amounts of Forssman antibody—the so-called naturally occurring Forssman antibody (1, 3, 4). Such immune or normal sera which contain Forssman antibody are toxic and often lethal when injected intravenously into animals whose tissues contain Forssman antigen (5, 6, 7, 8). The shock which is induced thereby is known as heterophile shock and is characterized by ruffling of hair, cough, respiratory distress, and convulsions.

Heterophile shock has been studied intensively in the guinea pig since the

early experiments of Friedberger and Castelli (5, 6), but although a considerable literature has accumulated about heterophile shock little mention has been made of desensitization. In one instance, it was stated that desensitization to heterophile shock could not be achieved (7), and in all other instances (5, 6, 8, 9) only the slightest degree of desensitization was demonstrated. It is the purpose of this paper to demonstrate that desensitization of the guinea pig can be effected to massive doses of the Forssman antibody.

MATERIALS AND METHODS

Preparation of Forssman Antiserum

Sheep blood, obtained from the abattoir and preserved in 3.8% sodium citrate in the ratio of 4 volumes of blood to 1 volume of anticoagulant, served as the source of Forssman antigen. The actual antigen injected into rabbits was a suspension of washed, boiled sheep erythrocyte stroma furnished by Mr. H. J. Rapp and prepared in accordance with a method outlined in his dissertation (10). The stroma suspension contained approximately 10 mg. of nitrogen per ml.

Three male albino rabbits (rabbits 435, 439 and 442) were injected intravenously with stroma according to the following schedule:

day	1 0.1 cc.
	3 0.2 cc.
	4 0.4 cc.
	6 0.6 cc.
	8 0.8 cc.
	10 1.0 cc.
	11 1.0 cc.
	13 2.0 cc.
	19 cardiac puncture
	20 cardiac puncture
	23 1.5 cc.
	25 1.5 cc.
	32 cardiac puncture

The sera obtained by cardiac punctures were pooled, and this serum pool was designated serum P. Part of the serum obtained from rabbit 439 was withheld from the pool and was designated serum 439. Three months later, rabbit 435 was immunized with stroma again, according to the following schedule:

day	1 0.1 cc.
	3 0.3 cc.
	4 0.4 cc.
	6 0.6 cc.
	8 0.8 cc.
	10 2.0 cc.
	13 cardiac puncture
	15 cardiac puncture

The sera obtained by cardiac punctures were combined and the serum so obtained was designated serum 435-II. Finally, the sera obtained by cardiac punctures of two normal male, albino rabbits were combined, and the serum so obtained was designated serum NRS.

All blood obtained from normal and immune rabbits was allowed to stand at room temperature for one hour and at 4°C for one hour before centrifugation at 0°C and 480 × gravity (2000 rpm). All sera were heated at 56°C for 30 minutes to inactivate complement. Sera were stored at −28°C. The toxicity of the stored sera did not appear to change over a period of months.

Determination of Hemolytic Antibody

The procedure of titration was developed by Croft (11) in accord with the observation (12) that it is desirable to base titration of hemolytic antibody on kinetic analyses rather than on end-point measurements. The method used in this study for the titration of hemolytic antibody is a modification of the procedure developed by Croft (11), devised by Rapp (10):

"standardized sheep erythrocyte suspension..... 0.5 ml.
diluted hemolytic antiserum..... 0.5 ml.

incubate 15 minutes at 37°C

1/7.5 normal guinea pig serum (24 $C'H_{50}$* per ml.)..... 0.25 ml.

incubate exactly 15 minutes at 37°C

'stop diluent'†..... 2.5 ml."

The mixtures were centrifuged and the optical densities of the supernatant fluids determined spectrophotometrically.

The amount of antibody present in 0.25 ml. of the immune and normal sera used in this study, expressed in terms of 50% hemolytic units (AbH_{50}), follows:

serum	hemolytic antibody (AbH_{50}/0.25 ml.)
NRS	22
439	36,000
P	33,500
435–II	60,000

The antibody obtained in response to the injection of washed, boiled sheep erythrocyte stroma satisfied the criteria presented earlier for the definition of the Forssman antibody, in that it not only lysed sheep erythrocytes but was absorbed *in vitro* by guinea pig kidney.

Determination of Toxicity

The volume of solution injected was never less than 0.5 cc. When less than 0.5 cc. of antiserum was indicated, this amount was diluted to a 0.5 cc. volume with physiological saline.

The 100% lethal dose was determined by injecting normal guinea pigs intravenously with 0.12 cc. of Forssman antiserum. If 0.12 cc. did not kill several consecutive animals within 30 minutes, 0.25 cc. was given a new series of animals; if the latter dose was uniformly fatal within 30 minutes, it was defined as the 100% lethal dose. Such was the case

* The complement levels of guinea pig serum are expressed in terms of 50% hemolytic units ($C'H_{50}$).

† 1 part 0.075 M aqueous $Na_3C_6H_5O_7 \cdot 2H_2O$ diluted with 4 parts 0.15 M aqueous NaCl.

with serum 439. If, as with serum P and serum 435-II, 0.12 cc. was uniformly fatal, 0.06 cc. was injected into several animals. In the case of serum P, 0.06 cc. was not uniformly fatal and 0.12 cc. was defined as the 100% lethal dose. In the case of serum 435-II, 0.03 cc. was not uniformly fatal but 0.06 cc. was; 0.06 cc. was defined as the 100% lethal dose.

Technique of Desensitization

The animals used in these experiments were male, albino guinea pigs weighing, with but few exceptions, from 300 to 400 grams. All injections were intravenous, and for this purpose veins of the ear, wrist, foot, posterior thigh and penis were employed. The guinea pigs were usually injected every 3 to 6 hours; occasionally, the interval between injections was as short as 2 hours and once was as long as 12 hours.

The initial injection was either one-fourth or one-half of the previously determined 100% lethal dose. Thereafter, gradually increasing amounts of antiserum were administered, but it was of utmost importance, in the early stages, to proceed towards the larger dosages cautiously, lest many animals succumb to typical heterophile shock. To this end, the initial dosage was generally repeated at the second injection, the initial dosage was not doubled until the third injection, and that dosage was repeated at the fourth injection. When desensitization was effected to the point where 4 to 6 LD were tolerated, the dosage of antiserum could be increased more rapidly. In all, from 6 to 9 injections were given each guinea pig.

Each injection was made with great care, for the extravasation of small amounts of Forssman antiserum caused severe erythema and necrosis. Since this was a frequent complication, the guinea pigs were anesthetized with ether when the more delicate ear and wrist veins were utilized. Anesthesia was not used in any instance for the important final challenging injection, however. For this injection, the foot, thigh or penile veins were used.

RESULTS

Thirty guinea pigs were desensitized to Forssman antiserum, in some instances tolerating as many as 80 LD intravenously with only the mildest symptoms of toxicity. Twenty-one normal controls in every instance died 2 to 30 minutes after the injection of 1 LD intravenously. The desensitization was achieved by the intravenous administration of sublethal doses and progressively increasing multiples of the lethal dose of Forssman antiserum every few hours in the manner stated above. Tolerance to 12 LD was achieved by desensitization in as short a period as 22 hours. The maximal possible tolerance is not known, for 80 LD represent a volume of 5.0 cc. of whole serum—a large volume when introduced intravenously into the 300 to 400 gram animal. Determination of the maximal tolerance awaits the concentration of antibody into a smaller volume.

Three immune sera were used in this study. Desensitized guinea pigs tolerated 2.0 cc. of serum 439 without symptoms, whereas 4 normal controls challenged at the same time died 3 to 20 minutes after injection of 0.25 cc. (Table I). Desensitized guinea pigs tolerated as much as 5.0 cc. of serum P and serum 435-II with minimal symptoms, whereas 11 normal controls challenged simultaneously died 2 to 20 minutes after injection of 0.12 cc. of serum

TABLE I

Desensitization as Effected with Serum 439

Animal	Amount of Serum Administered (cc.)															Response to Final Challenge	Max. No. Lethal Doses Tolerated
1	.25															died 20 minutes	
2	.25															died 20 minutes	
3	.25															died 3 minutes	
4	.25															died 3 minutes	
D-1	.12	.12				.25			.50			.75	1.0		2.0	none	8
D-2	.12	.12				.25			.50			.75	2.0			none	8
D-3	.12		.12		.25				.50		.75			2.0		none	8
D-4	.12		.12	.25			.50	.75		2.0						none	8
Hrs. after first injection	0	6	8	12	14	15	16	21	23	25	26	29	32	33	40		

P, and 6 died 5 to 10 minutes after injection of 0.06 cc. of serum 435-II (Tables II, III).

Since Forssman antiserum produces a marked local reaction when injected intradermally into a guinea pig (7), skin tests were performed with 0.2 cc. of serum 435-II in 3 desensitized and 2 normal animals (Table IV). The site of inoculation was barely discernible in the desensitized animals at one hour and was at most a pallid area with slight induration at 24 hours. Quite in contrast, the site of inoculation was mildly hemorrhagic in the normal animals within 5 minutes and was markedly hemorrhagic at one hour. Microscopic examination of the skin lesions at 24 hours showed widespread and severe inflammation, hemorrhage and necrosis in the normal animals and only slight inflammation in the desensitized animals.

One desensitized guinea pig (D-24) died between 7 and 13 hours after the final challenging dose. The cause of death was not clearly attributable to the Forssman antibody. This guinea pig was challenged with 80 LD of serum 435-II and exhibited mild symptoms from which he rapidly recovered (Table III). A skin test was performed 5½ hours later and when read at one hour it was completely suppressed. At no time did he appear ill, and when seen as long as 7 hours after the final challenging dose he presented none of the signs of heterophile intoxication (i.e., tachypnea, pulmonary edema, etc.). Thirteen hours after challenge with 80 LD, 7½ hours after skin-testing, he was found dead; the skin test was still suppressed. Autopsy revealed an intense gastric dilatation, and although microscopic examination of the lungs revealed slight perivascular edema the changes noted were not the intense ones usually seen with fatal heterophile shock. None of the guinea pigs that died from the effects of Forssman antibody showed gastric dilatation at autopsy.

To establish that the desensitizing factor is actually the Forssman antibody, ideally, one would absorb the antiserum with pure Forssman antigen. Since the pure antigen has never been isolated, one must be satisfied at present with

TABLE II

Desensitization as Effected with Serum P

Animal	Weight (gms.)	Amount of Serum Administered (cc.)																													Response to Final Challenge	Max. No. Lethal Doses Tolerated
5		.12																													died 4 minutes	
6		.12																													died 4 minutes	
7		.12																													died 4 minutes	
8		.12																													died 4 minutes	
9	310	.12																													died 2 minutes	
10	410	.12																													died 20 minutes	
11	300	.12																													died 3 minutes	
12	325	.12																													died 3 minutes	
13	350	.12																													died 3 minutes	
14	425	.12																													died 30 minutes	
15	390	.12																													died 2 minutes	
D-6		.03			.03					.12				.12					.25					.25			.75			tachypnea	6
D-7		.06			.06					.12					.12					.25			.25		1.0					tachyphea	8
D-8		.03			.03					.06							.06					.12			.25				1.0		none	8
C-1	310	.06	.06					.12			.12		.25				.50	1.5													none	12
D-12	345	.06			.06				.12				.12					.25				.75				1.5					none	12
D-13	340	.06			.06				.12				.12					.25				.75				1.5					none	12
D-14	330	.06			.06				.12				.12					.25				.75				1.5					none	12
0	325	.06			.06				.12				.12					.25				.75				1.5					none	12
C-2	290	.03		.06				.06			.12					.12			.25				.50					1.5			none	12
C-3	330	.03		.06				.06			.12					.12			.25		.25		.50					1.5			none	12
D-9	265	.03		.03			.06						.06				.12			.12					.25		1.0			2.0	ruffled hair, arched back	16
D-11	320	.06			.06				.12				.12					.25				.75				1.5			4.0		ruffled hair	32
D-15	320	.03	.03			.06			.06				.12				.12		.25		2.0				5.0						ruffled hair, nose scratching	40
D-16	304	.03	.03			.06			.06				.12				.12		.25		2.0				5.0						ruffled hair, nose scratching	40
D-17	314	.03	.03			.06			.06				.12				.12		.25		2.0				5.0						ruffled hair, nose scratching	40
Hours after first injection		0	4	5	6	7	9	10	11	12	13	14	16	17	18	19	20	22	23	24	25	26	27	29	30	31	32	33	34	35	37	38	46		

TABLE III

Desensitization as Effected with Serum 435-11

TABLE III

Desensitization as Effected with Serum 435-II

Animal	Weight (gms.)	Amount of Serum Administered (cc.)																Response to Final Challenge	Max. No. Lethal Doses Tolerated
16		.06																died 10 minutes	
17		.06																died 10 minutes	
18		.06																died 10 minutes	
19	450	.06																died 5 minutes	
20	550	.06																died 10 minutes	
21	348	.06																died 5 minutes	
D-18		.015	.015		.03		.03		.06		.06		.12		.25	1.0		none	16
D-19	330	.03		.03		.06		.06		.12		.12		.25			1.5	cough, ruffled hair, tachypnea, recovery	24
D-20	490	.03		.03		.06		.06		.12		.12		.25			1.5	cough, ruffled hair, tachypnea, recovery	24
D-21	470	.03		.03		.06		.06		.12		.12		.25			1.5	cough, ruffled hair, tachypnea, recovery	24
D-22	375	.03		.03		.06		.06		.12		.12		.25			1.5	cough, ruffled hair, tachypnea, recovery	24
D-23	350	.03		.03		.06		.06		.12		.12		.25			1.5	cough, ruffled hair, tachypnea, recovery	24
D-28	300	.03		.03		.06		.06		.12		.12		.25			1.5	none	24
D-24		.03		.03		.06		.06		.12		.12		.25			1.5	5.0	cough, ruffled hair, nose-scratching, recovery	80
D-25	320	.03		.03		.06		.06		.12		.12		.25			1.5	5.0	cough, ruffled hair, nose-scratching, recovery	80
D-26	300	.03		.03		.06		.06		.12		.12		.25			1.5	5.0	cough, ruffled hair, nose-scratching, recovery	80
D-27	300	.03		.03		.06		.06		.12		.12		.25			1.5	5.0	cough, ruffled hair, nose-scratching, recovery	80
Hours after first injection.....		0	7	8	11	13	16	17	20	23	26	28	32	34	36	38	39	43		

TABLE IV

Suppression of Skin Test in Desensitized Guinea Pigs

Time after Intradermal Injection of Antiserum	Desensitized Guinea Pigs*			Normal Guinea Pigs†	
	D-25	D-26	D-27	N-11	N-12
5 min.	no reaction	no reaction	no reaction	bluish discoloration	bluish discoloration
1 hr.	sl. residual swelling; no discoloration	sl. residual swelling; no discoloration	sl. residual swelling; no discoloration	1.0 x 2.0 cm. purple hemorrhage with gray-green halo	1.0 x 1.0 cm purple hemorrhage with gray-green halo
8 hrs.	sl. induration and pallor	sl. induration and pallor	sl. induration and pallor	1.2 x 2.0 cm., hemorrhagic	1.5 x 1.5 cm., hemorrhagic
24 hrs.	1.0 x 1.0 cm. pallor; sl. induration	1.0 x 1.0 cm. pallor; sl. induration	no lesion detectable	1.2 x 2.0 cm., hemorrhagic, sl. purulent	1.5 x 1.5 cm., hemorrhagic, sl. purulent

* 0.2 cc. serum 435-II injected intradermally 5½ hrs. after challenge with 80 LD.
† 0.2 cc. serum 435-II injected intradermally.

TABLE V

The Failure of Normal Rabbit Serum to Effect Desensitization

Animal	Weight (gms.)	Amount of Normal Rabbit Serum Administered (cc.)													Response to Challenge with Antiserum	Lethal Doses Serum P Administered
NRSD-1		.03	.06			.12		.12		.25	.25		.50*		died 1 minute	4
NRSD-2		.03	.06			.12		.12		.25	.25		.50	.50*	died 3 minutes	4
NRSD-3		.03	.06			.12		.12		.25	.25		.50	.25*	died 2 minutes	2
NRSD-4		.03	.03		.06		.06		.12		.12		.12*		died 1 minute	1
NRSD-5	300	.03		.06		.06		.12		.12	.25	.50		.25*	died ½ minute	2
NRSD-6	330	.03		.06		.06		.12		.12	.25	.50		.25*	died 4 minutes	2
Hrs. after first injection		0	4	5	8	10	13	14	18	19	24	29	30	35	36		

* Challenge with antiserum P.

less rigorous controls. For this reason, Forssman antiserum (serum P) was absorbed with an emulsion of guinea pig kidney; the absorbed serum was no longer toxic. The toxicity of antiserum treated exactly similarly with an emulsion of rat kidney (the rat contains no Forssman antigen) was in no way affected. Finally, 6 guinea pigs were subjected to an exactly similar program of injections as the 30 desensitized animals but were injected repetitively with normal rabbit serum instead of Forssman antiserum. At the conclusion of such a program, they were challenged with small amounts of Forssman antiserum. As can be seen in Table V, despite its slight content of Forssman antibody, normal rabbit serum offered no protection against Forssman antibody.

DISCUSSION

Heterophile shock is customarily studied by injecting Forssman antibody into guinea pigs, many of whose tissues contain Forssman antigen. It is generally agreed that heterophile shock, like ordinary anaphylactic shock, represents an antigen-antibody reaction (1, 3, 4, 6, 8, 13), but the precise relation of heterophile shock to ordinary anaphylactic shock is not clear, in view of features cited by many investigators suggesting that it is an entity distinct from anaphylactic shock. Although the clinical picture of heterophile shock characterized by ruffling of hair, nose-scratching, cough, respiratory distress, convulsions and death is very similar to that of ordinary anaphylactic shock, exudation of hemorrhagic, edematous froth from the nostrils of guinea pigs in acute heterophile shock is an almost constant feature. This is not characteristic of anaphylactic shock. Autopsy examinations of guinea pigs which have died from acute heterophile shock allegedly do not reveal distension of alveoli to the intense degree so characteristic of ordinary fatal anaphylactic shock, but, instead, examination of the lungs is said to reveal hemorrhage and edema (7, 14, 15, 16, 17). Hemorrhage and edema were prominent findings in the lungs of the animals that died from heterophile shock in the course of this study, but distension of alveoli was a more noteworthy finding than one would expect from the literature. That death in heterophile shock may not be due to bronchoconstriction as in ordinary anaphylactic shock is suggested by the evidence (17) that adrenalin and aminophylline are said to be ineffective in preventing death from heterophile shock, though well known to be effective in preventing death from ordinary anaphylactic shock. Furthermore, it is said (7) that the isolated guinea pig uterus, despite its content of Forssman antigen, will not respond by contraction to contact with Forssman antiserum in the Dale bath, quite unlike the classic anaphylactic uterus in contact with its sensitizing antigen. One cannot be certain, however, that the Forssman antigen said to be present in the guinea pig uterus (7) resides in the muscular layer, for the preparation used in establishing the presence of Forssman antigen in the uterus was apparently not free of peritoneum and endometrium. Insofar as we have been able to determine, Redfern's experiments (7) with the isolated guinea pig uterus have never been repeated.

Finally, of particular relevance to this study, Forssman and Fex (8) emphasize that, while in classic anaphylaxis one may develop a high degree of resistance to shock by means of desensitization, in heterophile shock one can never create a high degree of resistance by this means; resistance can be effected, they state, to "scarcely twice the acute lethal dose" (8). Others (5, 6, 9), using small numbers of animals, also demonstrated only slight degrees of resistance to heterophile shock. In each instance, these authors used but a single sublethal injection in attempting to effect desensitization, and in each

instance they achieved resistance to hardly more than 1 LD. Redfern (7) stated that even this degree of desensitization could not be achieved.

That desensitization to massive doses of Forssman antiserum can be effected is shown in this study. The rapidity with which desensitization can be established has not been investigated here, nor has the duration of the state of desensitization, but 3 guinea pigs tolerated 4 LD 48 hours after the standard program of desensitization was completed. It would appear, therefore, that the desensitized state may last at least 48 hours.

The role of complement in heterophile shock has not been adequately studied in the present experiments.*

SUMMARY

The present experiments demonstrate that desensitization of the guinea pig to Forssman antibody can be accomplished. In some instances, as many as 80 LD were tolerated intravenously with but slight and transient symptoms. The skin test in the desensitized animals was markedly, but not completely, suppressed.

ACKNOWLEDGMENTS

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* Blood complement levels were determined in a small number of guinea pigs by Dr. A. G. Osler according to the method of Osler, Strauss and Mayer (18). The levels were lowered in the 3 desensitized guinea pigs studied from values of 100, 136 and 146 $C'H_{50}$/ml. 1 hour before the program of desensitization with Forssman antiserum was begun to values of 10, 9, and 9 $C'H_{50}$/ml. respectively 2 hours after it was completed. In 3 guinea pigs treated exactly similarly with normal rabbit serum (NRS), the pre-treatment values were 160, 152, 184 $C'H_{50}$/ml. and the post-treatment values, 144, 153 and 168 $C'H_{50}$/ml. respectively.

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CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS DIAGNOSED AS IDIOPATHIC THROMBOCYTOPAENIC PURPURA

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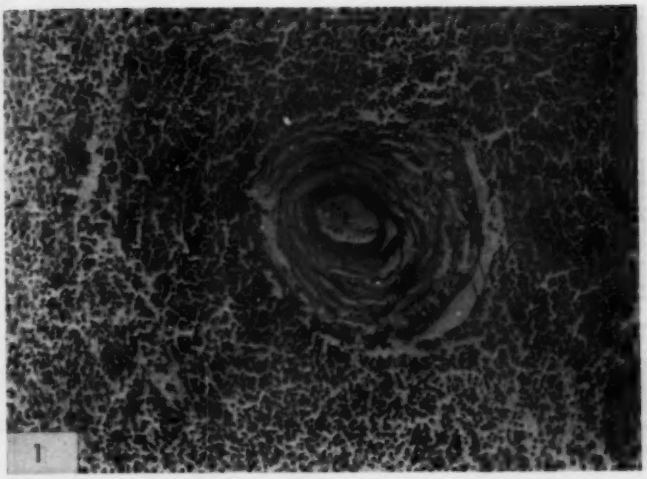
It is well known that either thrombocytopaenic or non-thrombocytopaenic purpura may be a manifestation of disseminated lupus erythematosus. It is the purpose of this report to point out that thrombocytopaenia and purpura may be the presenting symptom or dominant symptom of this disease, leading to the erroneous diagnosis of idiopathic thrombocytopaenic purpura, that is, thrombocytopaenia and purpura occurring in the absence of conditions which are known to be associated with thrombocytopaenia and purpura. Other symptoms of disseminated lupus erythematosus may not be recognized for months or even years following onset of the purpura. We have had occasion to study cases of thrombocytopaenic purpura in which the relationship to disseminated lupus erythematosus was established only at autopsy or on finding the characteristic histological lesion in the spleen removed at operation for what was thought to be the idiopathic type of thrombocytopaenic purpura. These cases demonstrate the importance of considering disseminated lupus erythematosus in all cases of thrombocytopaenic purpura.

The pathological lesion in the spleen that, when well marked, is generally regarded as pathognomonic of disseminated lupus erythematosus, is the "onion peel" fibrosis around arteries, particularly the small arteries, in the Malpighian bodies. This lesion, which was described by Klemperer, Pollack, and Baehr (1), consists in concentric rings of collagenous or hyaline connective tissue around small vessels in the Malpighian bodies (Figs. 1 through 8*). Neither the pathogenesis nor the manner of formation of this lesion is understood. While it is possible that this peculiar splenic lesion may be shown eventually not to be specific for disseminated lupus erythematosus, present information strongly supports the view that the lesion, *when well marked*, is pathognomonic of this disease. At least it has never been demonstrated to occur in well marked and unequivocal degree in any condition other than disseminated lupus erythematosus, or in any case in which the clinical and pathological findings were incompatible with disseminated lupus erythematosus. This splenic lesion is not found in all cases of disseminated lupus erythematosus, just as the characteristic dermal, endocardial, and renal lesions may be absent. Furthermore, the presence of this splenic lesion is evidence only of disseminated lupus erythematosus, which may or may not be associated with purpura.



EXPLANATION OF ILLUSTRATIONS

(Photographs by Mrs. Joan Bailey)

FIG. 1—Case 1. Perivascular "onion peel" fibrosis in a Malpighian body of the spleen removed at operation. This lesion is not very marked. (Surg. Path. 94361).

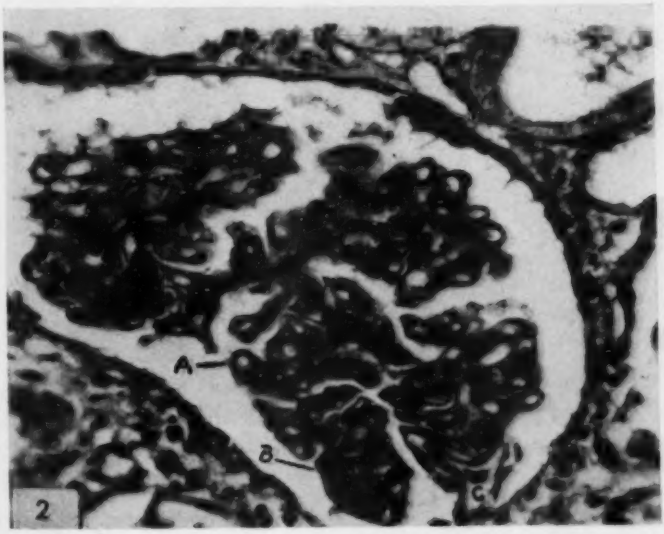


FIG. 2—Case 1. Renal glomerulus showing "wire loops" such as "A", a solid hyaline loop "B", and epithelial proliferation "C". (Autopsy 21193).

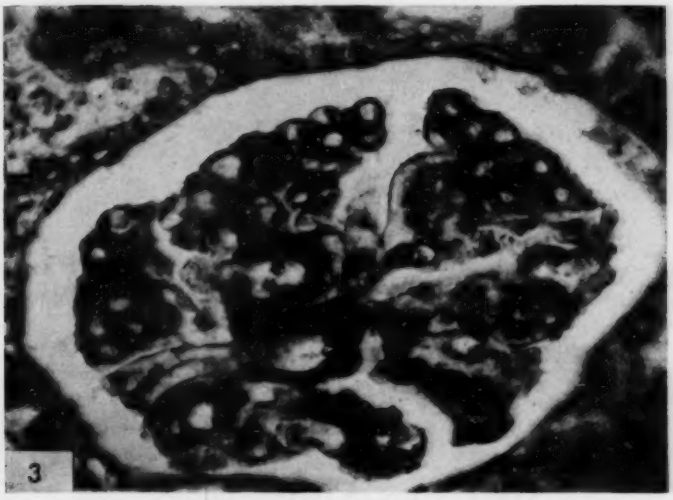


FIG. 3—Case 2. Renal glomerulus with marked thickening of basement membranes and "wire loops". (Autopsy 10834).

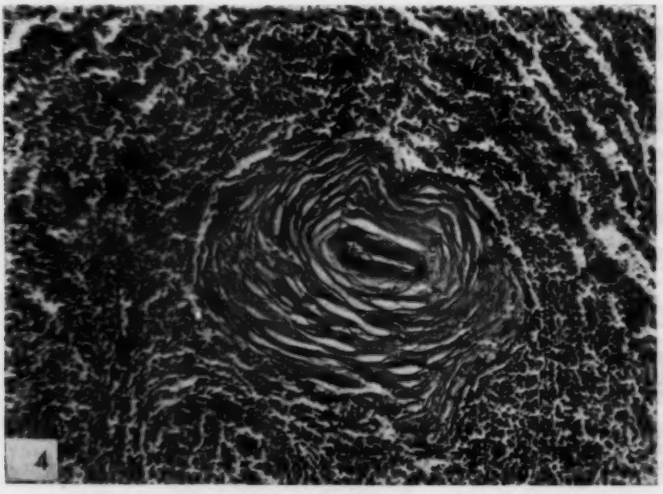


FIG. 4—Case 2. Marked perivascular "onion peel" fibrosis in a Malpighian body of the spleen. (Autopsy 10834).

It is interesting that in a case of "essential thrombocytopaenic purpura" reported by Kaiser (2) in which, at autopsy, the spleen showed "onion peel" lesions and no note was made in the autopsy report of the presence of other lesions of disseminated lupus erythematosus, a re-study of the autopsy sections shows the "wire loop" thickening of basement membranes (Fig. 3) that

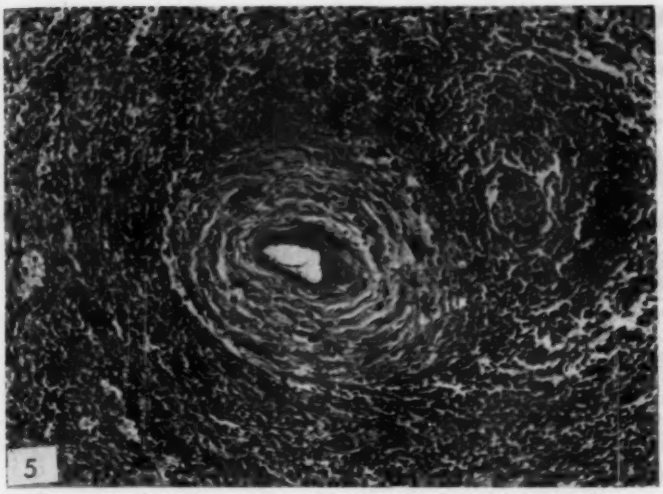


FIG. 5—Case 3. Perivascular "onion peel" fibrosis in a Malpighian body of the spleen. A few lymphocytes are seen between the rings of collagen. (Surg. Path. 84747).

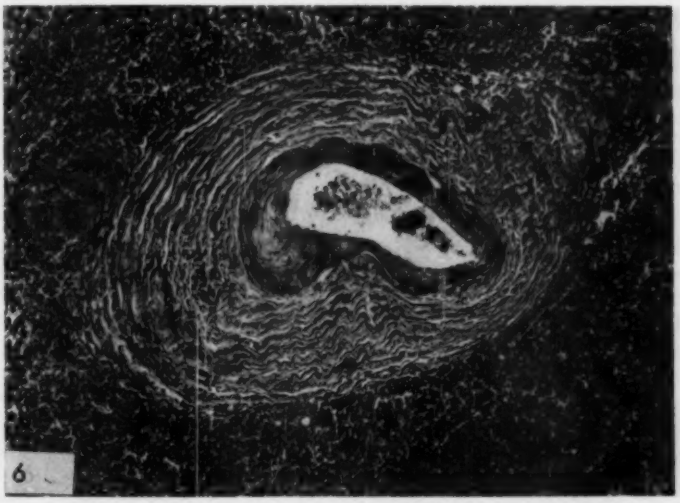


FIG. 6—Case 4. Marked perivascular "onion peel" fibrosis in a Malpighian body of the spleen removed at operation. (Surg. Path. 51-1616).

subsequently was shown to be a frequent manifestation of disseminated lupus erythematosus (3).

Case I. Hist. No. 47972. Autop. No. 21193.

This 11 year old negro girl came to the Johns Hopkins Hospital, May 21, 1946 because of intermittent bleeding from the nose and mouth of two months duration. At the age of

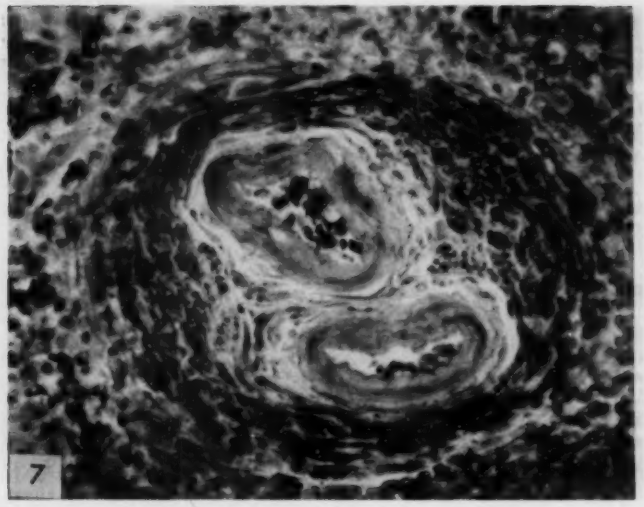


FIG. 7—Case 5. Perivascular "onion-peel" fibrosis in a Malpighian body of the spleen removed at operation. (Surg. Path. 50-5223).

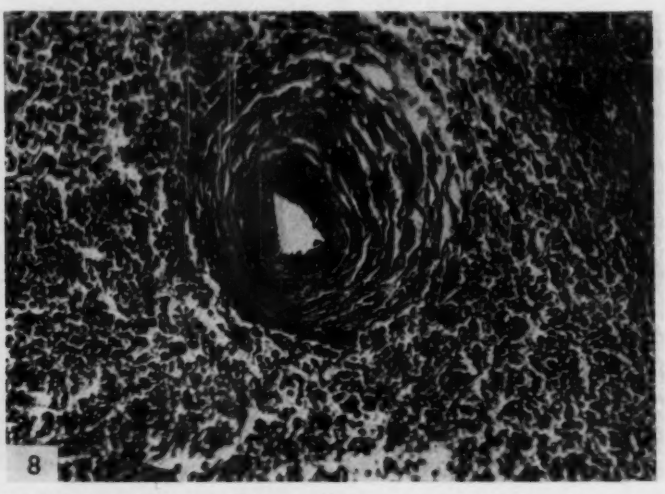


FIG. 8—Case 6. Perivascular "onion peel" fibrosis in a Malpighian body of the spleen removed at operation. (Surg. Path. 78643).

7 years she was found to have congenital syphilis which was treated for one year with arsenicals and bismuth. Her serology had remained weakly positive and she was considered "Wasserman fast". Her present illness started two months before admission when she started to ooze blood from her gums. At that time a tooth was extracted and she bled pro-

fusely from the socket for one week. She continued to bleed from the gums and started to have frequent nosebleeds. Three weeks before admission another tooth was extracted and she bled very profusely. She began to complain of occasional joint pains and abdominal pain. Two weeks before admission she developed petechial hemorrhages on her extremities which later spread to her body.

On physical examination the temperature was 99.2°F. the pulse 130, the respirations 24, and the blood pressure 110/80. The patient was well developed and well nourished. There were moderate pallor, generalized purpura, clotted blood in the mouth and nose, and blood was oozing from the gums. Non-tender generalized lymphadenopathy, a soft basal systolic murmur which was not transmitted, and a clear chest were found. The spleen and liver were just palpable at the costal margin. There were 2.53 million red blood cells per cmm., 7 grams of hemoglobin per 100 cc., 6,300 white blood cells per cmm. with a normal differential and 12,000 platelets per cmm. The bleeding time was 43 minutes; the clotting time was 23 minutes. No clot retraction was noted in 48 hours. The total serum proteins were 7.1 grams, with the albumen 4.2, and the globulin 2.9 grams per 100 cc. The diagnosis of idiopathic thrombocytopaenic purpura was made. Continuous bleeding from the mouth and nose necessitated numerous blood transfusions. On the ninth hospital day (May 30, 1946), the spleen was removed. Post-operatively the patient went into shock requiring blood transfusions. The following day she had a pericardial effusion. The platelets began to rise on the third post-operative day and were up to 270,000 on discharge, the ninth day following operation. The purpura did not recur and many subsequent blood studies revealed normal platelet counts.

The spleen removed at operation (Surg. Path. 94361) had a delicate capsule. Microscopically, the Malpighian bodies were hyperplastic. The small arteries in these showed "onion peel" periarterial fibrosis characteristic of disseminated lupus erythematosus (Fig. 1).

She was re-admitted almost two years later (March 17, 1948) with the complaint of swelling of the feet and eyes for one week. In the out-patient clinic she had been seen the previous year (April 21, 1947) complaining of painful swelling of the fingers and feet. The diagnosis of rheumatoid arthritis had been made. This had been treated symptomatically with aspirin. There had been recurrent flare-ups in the arthritis and she had developed slight deformities of her fingers. About the first of March a small red pimple appeared on the face just in front of the left ear. It became about the size of a nickel and was purple in color. Several similar lesions developed in the suprasternal notch. A week later, April 7, the ankles were noted to be markedly swollen. There was no associated pain. A few days later the eyelids were noted to be swollen in the mornings. The upper eyelids became excoriated. On physical examination, in addition to the soft painless ankle edema, circinate raised lesions on the left ear and cheek were noted. These had red borders and brownish atrophic appearing centers. Red tender skin was noted over a thenar eminence. Similar areas of apparently circumscribed lesions were found on the left palm. Generalized glandular enlargement was present. There was a soft apical systolic murmur. The blood pressure was 94/68. The fingers showed the spindle-shaped deformities of rheumatoid arthritis. The hemoglobin was 14.5 grams per 100 cc., the white blood cell count 7440 per cmm., with 65 per cent lymphocytes, and the platelets were 486,000 per cmm. The urine gave a 3 to 4 plus test for albumen. A few red blood cells and white blood cells were noted in the urine. The total serum protein was 4.2 grams with 1.2 grams of albumen and 3.0 grams of globulin per 100 cc. The cholesterol was elevated to 636 mgm. per 100 cc. The non-protein nitrogen, calcium, and phosphorus were normal. Urinary phenolsulfonephthalein test was normal, as was the urea clearance. She developed an erythema nodosum-like lesion in the left palm. On April 2nd it was noted that her urine was dark and this was found to be due to hemoglobinuria. Her hemo-

globin had fallen to 9 grams from 14.5 grams per 100 cc. two weeks previously. She had received plasma, but no blood transfusions. Repeated blood studies failed to incriminate any specific hemolysin. She developed ulcerated bleeding pustular plaques on the gums and buccal mucosa. The temperature had risen to 39°C. On the 17th of April a red papular eruption was noted over the trunk varying in size from 1 mm. to 2 cm. These had depressed dark centers. The facial lesions had acquired the "butterfly" distribution characteristic of lupus erythematosus. On March 23rd an inguinal lymph node biopsy was made. This showed only hyperplasia. On April 19th the skin rash was biopsied (Surg. Path. 48–1455). This showed hyperkeratinization of the surface epithelium with keratinized plugs in the hair follicles, and marked vacuolization of the cells of the basal layer. The rete pegs and skin appendages were atrophic. The collagen fibers of the dermis appeared swollen and there was a perivascular mononuclear cell infiltration in the dermis. The picture was characteristic of disseminated lupus erythematosus. She complained on April 22nd of generalized aching and stiffness of the joints. The temperature remained elevated. She became delirious. A pericardial friction rub appeared and there was pericardial effusion. The skin rash and edema had persisted. She died on April 24, 1948. The final clinical impression was lupus erythematosus, nephrosis, and hemoglobinuria.

The autopsy (21,193) showed the "wire loop" lesion of disseminated lupus in the glomeruli as well as focal glomerular epithelial proliferation (Fig. 2). The skin showed vacuolization of the cells of the Malpighian layer of the epithelium, hyperkeratosis, atrophy of the epithelium, and mononuclear cell perivascular infiltration, all characteristic of disseminated lupus erythematosus. In addition, the renal tubules were dilated and pigmented casts were found in them. There were multiple staphylococcal abscesses in the various organs, as well as a staphylococcal fibrinopurulent pericarditis and fibrinous pleurisy. The bone marrow was normal.

In summary, an eleven year old girl entered the hospital with purpura and thrombocytopaenia. The diagnosis of idiopathic thrombocytopaenic purpura was made and splenectomy was performed. The platelets promptly rose to normal, the purpura disappeared and did not recur. One year later she developed arthritis, diagnosed as rheumatoid arthritis. A year after this she developed the characteristic facial "butterfly" lesion of disseminated lupus erythematosus, and died from staphylococcal pyemia. The spleen, removed at operation, showed the "onion peel" periarterial fibrosis characteristic of disseminated lupus erythematosus and the kidneys, at autopsy, showed the "wire loop" thickening of the basement membranes of the glomeruli familiar in this disease.

Case II. Unit. No. 23565. Autop. No. 10834.

This 22 year old married white female came to the Johns Hopkins Hospital March 8, 1929 because of bleeding from the nose, mouth, vagina, and cutaneous ecchymoses of about one month duration. Her past health had been excellent. She had previously had no bleeding tendency. No drug history was elicited. Also no fever, chills, or chest pain had been present. There had been mild pain, in the joints at times in the past year. The temperature was 99.6°F., pulse 100, respirations 20, and blood pressure 120/70. There was clotted blood in the nostrils and mouth as well as generalized petechiae and ecchymoses. A soft apical systolic murmur and marked accentuation of the pulmonic second sound were noted. The tip

of the spleen was palpable. A few shotty, small, non-tender lymph glands were palpable in the neck. The uterus was enlarged. She was five months pregnant.

There were 2.54 red blood cells per cmm., 45 per cent hemoglobin, and 9,750 white blood cells per cmm. with 78 per cent polymorphonuclear neutrophils and no eosinophiles. Reticulocytes were 3.5 per cent. The platelet count was 50,000 per cmm. The bleeding time was 130 minutes with no clot retraction in 24 hours. The clotting time was normal. A trace of albumen and many red blood cells were found in the urine.

She was treated with transfusions. On the tenth hospital day after complaining of headache she gradually became stuporous and died on the fifteenth hospital day (March 23, 1929).

The final clinical impression was idiopathic thrombocytopaenic purpura with intracranial hemorrhage.

The autopsy (10,834) revealed widespread petechial hemorrhages in all the organs and a massive fresh hemorrhage into the right cerebrum. The uterus was enlarged and contained a 300 gram fetus which was normal grossly and microscopically. Characteristic of disseminated lupus erythematosus were widespread "wire-loop" lesions in the renal glomeruli (Fig. 3) and "onion peel" periarterial fibrosis around Malpighian body arteries (Fig. 4). In sections of skeletal muscle there were rare focal collections of perivascular mononuclear cells. There was terminal bronchopneumonia. None of the other organs showed any pertinent lesions grossly or microscopically.

In summary, a 22 year old woman, five months pregnant, entered the hospital with generalized purpura and thrombocytopaenia. She had had mild arthritis during the preceding year. She died of intracranial hemorrhage. The clinical diagnosis was idiopathic thrombocytopaenic purpura. At autopsy "wire loop" lesions were found in the renal glomeruli as well as "onion peel" periarterial fibrosis in the spleen, both of which lesions are characteristic of disseminated lupus erythematosus. She had a massive fresh hemorrhage into the right cerebrum.

Case III. History No. 274052.

This 39 year old white woman first had petechiae and spontaneous ecchymoses in January, 1942. The previous three menstrual periods had been profuse and prolonged. The generalized purpura was the only positive physical finding other than pallor. There were 4.22 million red blood cells and 3,050 white blood cells per cmm. with a normal differential count, and 41,000 platelets per cmm. It was thought she had thrombocytopaenic purpura. Dr. M. M. Wintrobe thought, however, the leucopenia was "a little disconcerting". The clinical and laboratory findings over a period of 8 months remained essentially the same. The bleeding time ranged between 8 and 14.5 minutes. Splenectomy was recommended by Dr. Wintrobe and for this operation the patient entered the hospital, October 8, 1942. The physical examination revealed essentially the above findings. The blood pressure was 110/65. The spleen was removed October 9, 1942. The platelets rose to 198,000 per cmm. and the bleeding stopped. The white blood cell count rose to 19,800 per cmm.

The spleen, removed at operation (Surg. Path. 84747) weighed 154 grams. Its capsule was delicate. Microscopically, the Malpighian bodies were not hyperplastic. There was marked "onion peel" perivascular arterial fibrosis in the Malpighian bodies (Fig. 5).

She was readmitted November 30, 1945 with an acute febrile illness of 36 hours duration. The history states that since 1943 she had had a skin eruption each summer over the face

which had been diagnosed as a manifestation of light sensitivity. In 1945 it had been suggested as being due to lupus erythematosus. At that time she was pregnant and underwent an abortion. The terminal illness in 1945 began 36 hours before admission with generalized malaise, anorexia and fever. There was pain in the muscles and joints and skin without localization. She felt chilly. The physical examination revealed a temperature of 100.4°F., pulse of 96 and blood pressure of 88/68. There was a skin rash of a purpuric nature in butterfly distribution on the face. The pigmentation in this area was impressive. There was an erythematous blush over the chest and abdomen. The heart was normal. There was dullness over the base of the right lung. However, no rales were present and the chest x-ray showed no pulmonic consolidation. She was thought to have acute lupus erythematosus. The red blood cell count was 6.43 million per cmm. and the platelet count was 42,000 per cmm. The white blood cell count was 12,600 per cmm. The non-protein nitrogen was 73 mgm. per 100 cc. The urine had a trace of albumen and a few red blood cells. The course was stormy. She became delirious. The rash on the face became more violaceous. A blood culture grew out type 12 pneumococcus, and similar organisms were found in the cerebrospinal fluid. It was thought she might have acute adrenal insufficiency and adrenal cortical extract was administered. She died December 2, 1945. No autopsy was performed. The final clinical impression was acute lupus erythematosus and pneumococcal meningitis.

In summary, a 39 year old woman entered the hospital with generalized purpura and thrombocytopaenia which was diagnosed idiopathic thrombocytopaenic purpura. Leucopaenia had been present for several months. Following splenectomy the platelets rose to normal, the purpura cleared and did not recur. Two years later she developed skin lesions which had the facial "butterfly" distribution characteristic of disseminated lupus erythematosus. One year later she died of acute disseminated lupus erythematosus and pneumococcal septicemia. No autopsy was performed. The spleen, removed at operation, showed the "onion peel" periarterial fibrosis characteristic of disseminated lupus erythematosus.

Case IV. History No. 274379.

This patient was a 61 year old house-wife who came to the Johns Hopkins Hospital, April 13, 1951 for evaluation of purpura. During hospitalization at this hospital in 1942 for pain in the back, she was found to have 3,200 white blood cells per cmm. with a normal differential count. The platelets and red blood cells were normal. However, in 1947 during a bout of herpes zoster she was told elsewhere that the platelets were low, but two years later they were said to be normal. She had taken numerous drugs such as bromides, salicylates, penicillin, and streptomycin. Although she stated she had always bled easily, she had undergone several operations uneventfully in the past twelve years.

Two months before her last admission she first noted a bleeding tendency, bleeding for several days from pin-pricks. She developed purpura, epistaxis and bleeding from the gums. At the site of injections she developed large hematomas. The right knee became painful, swollen, and discolored.

The temperature, pulse, and respirations were normal. The blood pressure was 180/100. Generalized purpura and ecchymoses and a large old hematoma surrounded the right knee. The only other significant physical finding was a harsh apical systolic murmur. The red blood cells were 3.5 million per cmm., the hemoglobin 9 grams per 100 cc., and the hematocrit was 30 per cent. The white blood cells were 4,400 per cmm. with a normal differential

count. The platelets were 12,000 per cmm. No "L.E." cells were found in appropriate preparations. The stool was tarry black. The prothrombin time was normal. Sternal marrow smears were interpreted as normal other than lack of platelet formation. The urine was grossly bloody, but otherwise normal. The diagnosis of idiopathic thrombocytopaenic purpura was made. On April 19, 1951, splenectomy was performed. Twenty-four hours later the platelets had risen to 154,000 per cmm. and the bleeding tendency rapidly disappeared. Post-operatively she had daily fever spikes and the pulse remained above 100 for six weeks. In the first week in May she developed physical signs of pneumonitis in the right base and also right costo-vertebral angle tenderness. These physical signs persisted and May 12, 1951 she developed a pericardial friction rub and the heart became enlarged to the left. One week later auricular fibrillation began and this arrhythmia quickly reverted to normal on quinidine therapy. Several days later she developed an erythematous rash over the chest. The pericardial friction rub and bilateral basal rales came and went. The temperature gradually returned to normal. On July 1, 1951, she was discharged because of difficulties at home. The final diagnosis was disseminated lupus erythematosus with thrombocytopaenic purpura, acute pericarditis, and hypertensive cardiovascular disease.

The spleen removed at operation (Surg. Path. 51-1616) weighed 300 grams. There were fibrous capsular adhesions. Microscopically, the Malpighian bodies were hyperplastic and in many of these the periarterial "onion peel" fibrosis characteristic of disseminated lupus erythematosus was present (Fig. 6).

Yearly letters from her since discharge state that her health has been good. There has been no arthritis or skin lesions. The purpura has not recurred.

In summary, a 61 year old woman entered the hospital with purpura and thrombocytopaenia. Leucopaenia had been present for nine years. She was hypertensive and had a harsh systolic apical murmur. The diagnosis of idiopathic thrombocytopaenic purpura was made and splenectomy performed, following which the platelet count returned to normal and the purpura subsided. Post-operatively there was prolonged daily fever spikes, tachycardia, auricular fibrillation, pericarditis, and "pneumonitis". A transient rash developed over the chest. The pathological findings of periarterial "onion peel" fibrosis in the spleen, removed at operation, and the post-operative course, prompted the final diagnosis of disseminated lupus erythematosus. A three year follow-up (by letters) reveals no subsequent symptoms attributable to disseminated lupus erythematosus.

Case V. History No. 556044.

This 37 year old white woman first came to the Johns Hopkins Hospital, November 8, 1950 because of purpura. She gave a history of first noting "black and blue marks" on the skin in 1941. Menorrhagia began about the same time. Occasional nose bleeds and bleeding from the gums were also noted. She became pregnant in 1942. During the pregnancy she continued to develop "black and blue" marks. The delivery was not associated with undue bleeding. In the following years nose bleeds, purpura, and excessive menstrual bleeding recurred frequently. In the spring of 1950 she developed subungual hemorrhages of both great toes. This prompted a blood study in another hospital and she was told that the platelet count was low. Occasional excessive menstrual bleeding, bleeding from the gums and epistaxes had occurred in 1949. For many years she had developed hives from eating

citrus fruits, chocolate and nuts. She had had mild psoriasis since the age of 15 years. She occasionally had migraine headaches. The physical examination was negative other than old ecchymoses on the hips and legs. A typical psoriatic lesion was present over the right knee. The blood pressure was 116/65 and the temperature 98.6°F. The red blood cell count was 3.7 million per cmm. the hemoglobin 10.6 grams per 100 cc. and the platelets 47,000 per cmm. The tourniquet test was positive. The white blood cell count was 6,100 per cmm. The bleeding time was 5 minutes, the clotting time 2.5 minutes. On sternal marrow aspiration the few megakaryocytes seen did not seem to be forming platelets. The diagnosis of idiopathic thrombocytopaenic purpura was made. Splenectomy was accomplished December 29, 1950. Adhesions were found around the spleen. One week later the platelets were 200,000 per cmm. There was no further bleeding during her convalescence and no further information is available.

The spleen, removed at operation (Surg. Path. 50-5223), weighed 110 grams. Microscopically, the germinal centers of the Malpighian bodies were hyperplastic and in many of these the periarterial "onion peel" fibrosis characteristic of disseminated lupus erythematosus was present (Fig. 7).

In summary, a 37 year old woman entered the hospital with generalized purpura and thrombocytopaenia which had recurred for nine years. Splenectomy relieved the thrombocytopaenia and purpura. There has been no follow-up. The spleen removed at operation shows onion peel periarterial fibrosis characteristic of disseminated lupus erythematosus.

Case VI. History No. 207012.

This 24 year old white female had the chief complaint of nosebleeds and spots in the skin on her admission to the Johns Hopkins Hospital, July 8, 1940. She had had mild hives at times since childhood, but these had never required treatment. Five weeks before admission she noticed small red spots on the legs. The gums also had a tendency to bleed. One week prior to admission the left knee suddenly became tender, swollen, red and hot. This subsided in about five days. On admission the temperature was 100°F. the pulse 96, respirations 20, and blood pressure 120/70. The body was covered with petechial hemorrhages, the gums were bleeding, and clotted blood filled the nostrils. The eye grounds were normal. Generalized glandular enlargement was noted. The heart and lungs were normal. The liver and spleen were not felt. The red blood cell count was 3.38 million per cmm., the hemoglobin 11.2 grams per 100 cc., the hematocrit 31.5 per cent, the white blood cell count 5,200 per cmm., the icteric index was 5 units, and the sedimentation rate was 15 mm. The platelets were below 50,000 per cmm. The tourniquet test was very strongly positive. The bleeding time was longer than 14 minutes, the coagulation time was 11 minutes, and the prothrombin time was 8 minutes. The diagnosis of essential thrombocytopaenic purpura was made and transfusions of fresh blood were administered. Because no improvement occurred, splenectomy was performed July 17, 1940. The following day the bleeding time had risen to 2 minutes. The platelets did not increase in number until three days later when 300,000 per cmm. were present. On the second post-splenectomy day the purpura began to clear and there was no further bleeding tendency until the terminal illness.

The spleen removed at operation (Surg. Path. 78643) measured 12 x 8.5 x 4 cm. There were fibrous capsular adhesions. The Malpighian bodies were hyperplastic and in these the perivascular "onion peel" fibrosis characteristic of disseminated lupus erythematosus was present (Fig. 8).

In 1950, ten years later, the patient came in for re-evaluation. No further bleeding tendency had been noted. For the past six years there had been intermittent mild arthritis in the knees, but in no other joints. The physical examination revealed only a soft blowing, not transmitted, apical systolic murmur. The blood pressure was 110/70. No "L.E." cells were found on blood smear from oxalated blood. The red blood cell count 4.7 million per cmm., the white blood cell count was 10,750 per cmm., and platelets were 310,000 per cmm. On June 7, 1953, the patient was brought to the hospital moribund and she died shortly thereafter. There was generalized purpura and the neck was stiff. The purpura had been present 6 days. No other history was obtainable. This was interpreted clinically as acute recurrent purpura probably with intracranial hemorrhage. No autopsy was performed.

In summary, a 24 year old white woman entered the hospital with purpura and thrombocytopaenia. One week previously there had been arthritis in the left knee. The diagnosis of idiopathic thrombocytopaenic purpura was made and splenectomy was performed, following which the platelet count returned to normal and the purpura disappeared. Ten years later she was again seen and arthritis had been present for six years. Three years after this hospital visit she was brought to the hospital moribund with generalized purpura. No autopsy was performed. The spleen, removed at operation, showed the "onion peel" periarterial fibrosis characteristic of disseminated lupus erythematosis.

DISCUSSION

These six cases were all diagnosed clinically as idiopathic thrombocytopaenic purpura, and the diagnosis of disseminated lupus erythematosus was established only following splenectomy or at autopsy. Several years ago, in clinical pathological conferences in this hospital, attention was drawn to the fact that the spleens of some of the patients who were splenectomized for what was regarded clinically as idiopathic thrombocytopaenic purpura, showed the lesion characteristic of disseminated lupus erythematosus. Since then the possibility of disseminated lupus erythematosus has always been seriously considered clinically in cases of thrombocytopaenic purpura in this hospital. We have, therefore, in our surgical pathology files numerous other more recent cases of thrombocytopaenic purpura in which the "onion peel" lesion of disseminated lupus erythematosus is present in the spleen. These cases are not included in this report, as disseminated lupus erythematosus was considered in the clinical differential diagnosis of the purpura. In some of these cases, however, it was impossible definitely to establish this diagnosis prior to splenectomy. The presence of disseminated lupus does not necessarily contraindicate splenectomy. Indeed the thrombocytopaenic and purpura may be alleviated as in cases I, III, IV, V, and VI.

SUMMARY

Six cases are presented which were regarded clinically as idiopathic thrombocytopaenic purpura. The diagnosis of disseminated lupus erythematosus was

established at autopsy, or on finding characteristic histologic lesions of this disease in the spleen following splenectomy, or by the appearance of frank clinical evidences of disseminated lupus erythematosus subsequent to splenectomy. The importance of considering disseminated lupus erythematosus in all cases of thrombocytopaenic purpura is emphasized.

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE THE JOHNS HOPKINS MEDICAL SOCIETY

February 14, 1955

A HEMORRHAGIC DISORDER FOLLOWING WHOLE BLOOD TRANSFUSIONS

JULIUS R. KREVANS AND DUDLEY P. JACKSON

Twenty-seven adult patients and 5 newborn infants who received one or more whole blood transfusions were studied. Thrombocytopenia was observed in all 5 of the infants following exchange transfusions for erythroblastosis fetalis, and 2 developed clinical evidences of abnormal bleeding. All 14 of the adult patients who received from 5,000 ml. to 20,500 ml. of whole blood within a 48 hour period developed thrombocytopenia following the transfusions, and 11 developed clinical evidences of abnormal bleeding. All 14 had some degree of shock, and in 8 severe protracted shock was noted, which ultimately was resistant to further transfusions and to the administration of nor-epinephrine. Seven of the 14 developed severe bleeding which contributed significantly to morbidity and mortality, and 4 displayed moderate bleeding manifested by cutaneous petechiae, mild hematuria, or slightly excessive bleeding from the operative site. Other studies of hemostatic function were performed in 7 of the patients who developed abnormal bleeding. It seemed clear that the abnormal bleeding was due to thrombocytopenia. Fibrinogenopenia was not the cause of the abnormal bleeding, and was encountered in only one instance. Evidence of increased fibrinolytic activity was not encountered, and no circulating anticoagulant was detected. Some of the 13 adult patients who received less than 5,000 ml. of whole blood within a 48 hour period developed mild thrombocytopenia, but none developed evidences of abnormal bleeding.

The thrombocytopenia that was observed in these patients was related to the amount of whole blood transfused and the rate of infusion. The mechanism for the production of the thrombocytopenia is not known. It has been shown that normal blood contains a thrombocytopenogenic factor. It is possible that when large amounts of blood are administered this factor may be of importance in the production of thrombocytopenia. In addition the recipient's platelets may be diluted by the administration of bank blood which is deficient in platelets.

ANTEROLATERAL CERVICAL DISC REMOVAL AND INTERBODY FUSION FOR CERVICAL DISC SYNDROME

ROBERT A. ROBINSON AND GEORGE W. SMITH

The result of intervertebral disc degeneration at C 5–6, C 6–7 and C-7–T-1 levels was described in detail by Dr. Robinson. It was pointed out that as the disc ages degeneration of the disc occurs characterized by loss of water, loss of mass, an increased proportion of collagen fibers to mucopolysaccharide components, and thickening of the annulus fibrosis, with breaks in the cartilage plates which confine the disc inferiorly and superiorly. Such changes are those found not only with aging but when disc degeneration occurs in the younger age group. Following narrowing of the disc space the neuroforamen becomes smaller by encroachment of the pedicles; the facet joints become compressed; and spurs form on the posterior aspect of the vertebral bodies and the edges of the facet joints. Thus the neuroforamen is decreased in size. Interesting observations by other investigators have shown

that disc material protruded through a weakened annulus fibrosis may be resorbed. Evidence by other investigators that bony spurs develop under the stimulus of motion at an area of disc degeneration was noted. The authors applied this information in devising a surgical procedure for relieving pressure on the cervical nerve roots.

Dr. George Smith described the operative procedure as worked out on animals and then as applied to patients. The cervical spine is approached through an antero-lateral approach, the degenerated disc material remaining in the involved intervertebral space is removed under direct vision. The vertebral bodies are then separated as widely as the anterior and posterior longitudinal ligaments allow and a block of bone is placed in the intervertebral space.

The process of spur formation may be halted by anterior body fusion and possibly regress to relieve nerve root compression. Stopping motion of the spurs should decrease nerve root irritation. The widening of the intervertebral space when it can be obtained should immediately relieve some nerve root compression. By removing all degenerated disc material that remains in the disc space only that material that has already protruded need be removed by cellular activity in the spinal canal. Thus the time over which there would be active resorption of slowly protruding nuclear material would be markedly shortened.

It was pointed out that this operation had particular advantage in those cases in which the person had already had a facetectomy and foraminotomy on one side of the cervical sp ne with subsequent development of pain in the opposite arm and shoulder due to nerve roiot compression of the contralateral cervical root at the level of the first operation. Secondly, it was felt that this procedure prevented manipulation of the structures in the spinal canal and avoided in that way any possible surgical trauma to the spinal contents.

The clinical data on eight patients were presented. The follow-up on the oldest patient was only one year. It is too early to evaluate the final result on many of the patients. However, of the eight patients, three had excellent results with complete relief of discomfort and had returned to their normal activities; two had good results, that is they were able to return to work but still had some residual discomfort in their shoulder and arm. Two patients had poor results and the patient last operated did not have a long enough follow-up to make any estimate of the final result. In two cases there was a vocal cord paralysis, one of which cleared-up in approximately eight weeks, and the other one had not cleared-up two months after operation at the time this report was presented.

ON SUBARACHNOID BLEEDING: AN APPRAISAL OF TREATMENT

J. W. Magladery

There exists currently considerable diversity of opinion regarding optimal means of handling patients presenting with subarachnoid bleeding. During the past seven years, in this hospital, 198 such patients have been treated in a conservative fashion. In an additional 37, definitive operations were undertaken at various intervals after bleeding. The results obtained in the two groups were compared in terms of mortality, and also condition of survivors. The efficacy and risk of angiography was studied, as judged by the 90 patients in whom it was performed.

Based on this series, it was indicated that angiography plus definitive operations had so far proven too dangerous to be considered during the first day following bleeding. During the first week these combined procedures must need carry a mortality rate of less than 20 per cent, and no added disability, in order to compare favorably with conservative handling. Between the first and third weeks, this surgical objective must be lowered to less than

12 per cent to be considered effective therapy. In this series, these goals were not met. It was indicated that, whereas the present results do not conclusively lead to rejection of operative intervention in the treatment of subarachnoid bleeding, they provide nothing to support its use. A plea was made for further well-documented comparative reports from other centers in order to provide a more adequate picture of the effectiveness and potential dangers to be anticipated from interim operations on patients who had previously survived subarachnoid bleeding.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Recent Developments in Psychosomatic Medicine. Edited by ERIC D. WITTKOWER AND R. A. CLEGHORN. 495 pp., $10.00. J. B. Lippincott Co., Philadelphia, Pa.

It is a privilege to review this significant book. Superlative descriptions frequently appear to the point of banality in book reviews, but this volume really is superlative. The authors have selected a wide range of material, and have composed a first section on general aspects of the subject. Chapter One traces some of the main historical lines of theory and research which are bringing medicine toward a unitary theory. The authors point out that this process is still in the groping stage. Starting with Freud and Abraham, an explanation is given of the basic psychoanalytic theory and the various conceptual models of mind-body relationships by Freud, Ferenczi, Klein, Garma, Dunbar, Alexander, Kubie, Margolin, Grinker, Wolff, Ruesch, and Halliday. There is a stimulating chapter by Dr. Kubie on the specificity of the psychosomatic reactions. A thoroughly documented historical chapter traces the people, the scientific thinking, and advances made in this field. Subsequent chapters are devoted to research, methodology, and the philosophy of psychosomatic research. There is a review of the Limbic system, otherwise called the "smell brain" or rhinencephalon. Recent interest in this relatively unknown part of the nervous system has brought about new theories as to the mediation of the emotional and sensory experience of the human being. Dr. Margolin's chapter on psychotherapeutic principles presents ideas of wide clinical interest, reminding one of the intuitive empirical methods used by Wier Mitchell, as well as some contemporary internists.

The second section deals with specific problems, chapter by chapter, considering psychosomatic theory and empirical data relative to various organ systems. Then follow chapters on venereal disease, pediatrics, and one of particular interest to psychiatrists on psychosomatic disease and psychosis. There are also chapters on disablement, battle stress, and finally psycho-social aspects of psychosomatic medicine. These chapters are well-documented with the work of many outstanding people in various fields. The authors have chosen productions of certain talented and highly informed people, trained in psychiatric medical knowledge both specifically and in the broadest sense. They recognize that there are many others who have done comparable work but who have not been included.

This book represents a significant milestone in a field which is and has been rapidly advancing over the past quarter-century. The authors present an approach toward a unitary biological theory of disease and health. The influences of Sigmund Freud and Adolph Meyer are strongly shown, not only in the work presented and referred to, but in the people with their training who have produced it. Important work of men in other disciplines is obvious in this volume, particularly those in internal medicine, physiology, surgery, public health and dermatology, to mention only a few. The impression gained from the book is that the work being done in this field is becoming much more humanistically scientific. Obsessive, rigid thinking to provide labored rationality, particularly in psychosomatic medicine, where so little is known and the facts are so complex, is being attentuated. There are many controversial ideas to which the authors have not hesitated to expose the reader. The only improvement suggested is that there be more of this book. Anthropology, particularly cultural anthropology, has been mentioned in passing. A few authors are cited, but a chapter might well be devoted to this subject. In this reviewer's opinion, more space might be devoted to the ideas of Paul Schilder whose contributions are briefly treated. Margolin mentions the patient-physician relationship and its importance in the three methods of therapy: pharmacological, surgical, and psychological. What goes on in the patient-doctor "transactions" which promotes or retrards improvement in the patient's health and effectiveness? The authors might well have provided more on this fascinating subject, which is a preoccupation of many interested in psychosomatic medicine and medicine in general.

This book deserves careful scrutiny by any medically informed person, independently of his specialty, his interest, or his point of view.

WILLIAM T. DIXON

Textbook of Operative Surgery. By ERIC L. FARQUHARSON. 853 pp., $15.00. E. & S. Livingstone Ltd., Edinburgh and London. The Williams & Wilkins Co., Baltimore, Md.

Mr. Farquharson's stated purpose in his work was to provide a one-author, one-volume operative text written from the point of view of the general surgeon. The book is directed toward the physician in the early phase of surgical training and to the general surgeon who is called upon to perform a specialized procedure unfamiliar to him. It is, in these respects, somewhat unique since many of the texts published at present are multiple-authored and oriented to a higher level audience.

The scope of the book is large and includes general surgery, plastic surgery, neurosurgery, thoracic surgery, orthopedics and urology. The author considers many aspects of each problem, including anatomy, diagnosis, therapy and operative indications as well as technique. The illustrations are many and seem accurate. The paper is of satisfactory quality and the print is of good size.

It must be obvious that despite its 850 pages the book cannot cover with any thoroughness the encylopaedic list of subjects considered. These range from knot-tying and blood transfusion to the surgical correction of tracheo-esophageal fistulae. The author has attempted to encompass so much in a single volume that his consideration has necessarily been of superficial nature. It would seem an almost insuperable problem to adequately cover so many aspects of such a wide field of subjects in a single volume. In addition, the therapeutic methods advocated are sometimes open to question. For example, vein stripping is mentioned only to be discarded in the discussion of varicose veins. Again, quadruple ligation is inferred to be the procedure of choice in the treatment of arteriovenous fistulae. Restorative techniques are briefly mentioned but are described only as being "occasionally . . . possible". It is inconceivable that the group to whom this book is specifically directed would gain from this discussion the impression that restoration is indeed the procedure of choice whenever possible. Other similar situations are found.

This book may be of some value within the group to whom it is directed. This group, however, is sharply limited. The scope of consideration is too broad for those who have not yet begun surgical training, yet the discussions are too limited to be of value to the house officer beyond the earliest phase of training. It is the reviewer's opinion that this book will not prove to be a significant addition to the already large list of surgical texts.

JAMES R. CANTRELL

Renal Function. Transactions of the Fifth Conference October 14, 15 and 16, 1953. Edited by STANLEY E. BRADLEY. 218 pp. $3.75. The Josiah Macy, Jr. Foundation, New York, N. Y.

The Transactions of the Fifth Macy Conference on renal function have been recorded in their customary fashion. In contrast to their immediate predecessors, the topics considered in this book should appeal to a more catholic group of readers. Certain factors concerned in the pathogenesis and therapy of the nephrotic syndrome and acute renal failure were discussed by Dr. J. A. Luetscher, Jr. and Dr. G. M. Bull. Dr. B. F. Miller spoke of the problem of kidney transplantation in a manner which emphasized the increasing approximation of the homologous transplant technique to practicability.

Most of this material can be found elsewhere in the scientific literature. The main value of the conference record resides in the informal comments which were provoked by the aforementioned brief presentations. Of particular interest was the evidence offered by Dr. Bott which indicated tubular secretion of potassium and the discussion concerning several factors which are apparently involved in regulating the volume of the body fluid compartments.

ALBERT H. OWENS, JR.

Harrison's Principles of Internal Medicine, 2nd edition. Edited by T. R. HARRISON, RAYMOND D. ADAMS, PAUL B. BEESON, WILLIAM H. RESNIK, GEORGE W. THORN AND M. M. WINTROBE. 1790 pp., student 1 vol. ed. $16.00, professional 2 vol. ed. $12.00. The Blakiston Co., New York, N. Y.

The success of this publication is attested somewhat by the number of printings made since its appearance in August, 1950. The current (second) edition adds 150 pages of text to the previous one. Although there has been extensive revision of many chapters the basic pattern of the original arrangement of material has been retained. The main general groupings are (1) cardinal manifestations of disease, (2) basic mechanisms of disease and (3) specific disease processes. A new section devoted to general therapeutic measures in the case of a gravely ill patient has been added.

The grouping of information under manifestations, mechanisms and etiological factors in disease allows various observers to write about different facets of the same entities. In so doing much more information is made available to the reader. For example, blood groups, isoantibodies and inter- and intra-group transfusion reactions are discussed in three different sections. Although the arrangement of material necessitates some leafing through the book, the amount of information obtainable on any one of a wide variety of clinical problems justifies the slight inconvenience. Fortunately the cross-indexing is extensive.

Even with the best text-book a critical reader may find a few minor objections. The following are examples. This reviewer doesn't think the expense of penicillin in amounts of 12 million units a day is any legitimate deterrent to its use in the treatment of pneumococcal meningitis as stated on page 852. Diseases of the mouth and skin are neglected. Although the bibliography for the section on Actinomycosis is up-to-date, the references are actually poor ones and mention of Cope's book is omitted. The toxic effects of stilbamidine are not mentioned in the therapy of blastomycosis or multiple myeloma. There are rather frequent

typographical errors. The appropriateness of the use of such an expression as "positive Levinson test" (page 975) is debatable. Occasionally apparent contradictions occur: for example, on page 706 it is stated that acromegaly causes hypercalciuria but on page 406 urinary excretion of calcium is said to be decreased in acromegaly.

Fortunately two errors made in describing the action of vitamin D on page 681 in the first edition have been corrected on page 415 in the current edition.

The inclusion of a table of the normal ranges of laboratory values of clinical importance would be helpful for the medical student.

This is an excellent text and is highly recommended.

PHILIP F. WAGLEY

Peripheral Vascular Diseases, 2nd edition. By EDGAR V. ALLEN, NELSON W. BARKER AND EDGAR A. HINES, JR., with associates in the Mayo Clinic and Mayo Foundation. 825 pp., $13.00. W. B. Saunders Co., Philadelphia, Pa.

The second edition of "Peripheral Vascular Diseases" by Allen, Barker and Hines is a worthwhile and timely publication. During the interim of eight years since the first printing, great advances have been made in this field. These have been interwoven in the text and much obsolete material deleted.

A chapter is devoted to each disease or group of diseases of arterial and venous origin. The chapters are logically and thoroughly developed. The diseases are discussed from the point of view of historical background, etiology, pathology, symptoms, findings and treatment. The presentations of the vasospastic disorders and Burger's Disease are particularly good.

The last section is devoted to surgical treatment. Each aspect is discussed by men most active in that branch at The Mayo Clinic. The field is covered broadly yet in detail and is presented without bias.

In summary the book is a well written and edited volume based on a wealth of clinical experience. It is well illustrated. The student, physician and specialist alike should profit from this edition.

JOHN N. CLASSEN

Pediatric Diagnosis. By MORRIS GREEN AND JULIUS B. RICHMOND. 436 pp., $10.00. W. B. Saunders Co., Philadelphia, Pa.

In the Preface to *Pediatric Diagnosis*, Drs. Green and Richmond state that they are "concerned with helping students and practitioners to increase their diagnostic skill through a systematic and integrated approach to patient study that can be readily applied at the bedside or in the office." To accomplish this purpose, the book is divided into four sections. Section I is a fatherly sermon on the taking of a pediatric history dealing mainly with the establishment of rapport between physician and parents. Section II deals with the physical examination, describing both the normal and abnormal findings in each organ or region of the body and reviewing the developmental maturation of each organ. In section III, the signs and symptoms of disease are listed with brief notes on the various conditions causing same. Section IV, entitled "Health Supervision", is concerned with preventive pediatrics not only as applied to physical health, but also placing much emphasis on the handling of a child psychologically. There is an appendix consisting of detailed tables of body measurements in relation to age.

There is a great deal of useful and interesting information in more-or-less outline form included in the text, but it is the kind of information with which any qualified pediatrician should be moderately well acquainted. The chief usefulness of this book, in the opinion of

this reviewer, is for medical students learning the fundamentals of pediatrics and for general physicians not wholly familiar with the vagaries of both normal and abnormal conditions in children but faced with a clinical problem in this age group. To such medical men, *Pediatric Diagnosis* would be a most useful tool, and so the authors' purpose, as stated in the preface, is adequately fulfilled.

JOHN L. PECK

BOOKS RECEIVED FOR REVIEW

Adrenal Cortex. Transactions of the Fifth Conference, November 4, 5 and 6, 1953. Edited by ELAINE P. RALLI. 187 pp., $3.75. The Josiah Macy, Jr. Foundation, New York, N. Y.

Connective Tissues. Transactions of the Fifth Conference, February 8, 9 and 10, 1954. Edited by CHARLES RAGAN. 222 pp., $4.25. The Josiah Macy, Jr. Foundation, New York, N. Y.

Die Bronchographie. By ERNST STUTZ AND HEINZ VIETEN. 250 pp., Ganzleinen DM 66. ($15.70.) Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Fractures in Children. By WALTER R. BLOUNT. 279 pp., $9.50. The Williams & Wilkins Co., Baltimore, Md.

Grundriss der Allgemeinen Zoologie. By ALFRED KÜHN. 281 pp., Ganzleinen DM 16.50 ($3.95). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Heart. A Physiologic and Clinical Study of Cardiovascular Diseases, 2nd edition. By ALDO A. LUISADA. With a Foreword by Herrman L. Blumgart. 680 pp., $15.00. The Williams & Wilkins Co., Baltimore, Md.

Kritik der Psychosomatik. By HANS JÖRG WEITBRECHT with a foreword by Kurt Schneider. 114 pp., kartoniert DM 12 ($2.85). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Operative Cholangiographie. Technik, Diagnostik, Praxis. By WALTER HESS with a foreword by R. Nissen. 201 pp., Ganzleinen DM 42. ($10.00). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Reactions with Drug Therapy. By HARRY L. ALEXANDER. 301 pp., $7.50. W. B. Saunders Co., Philadelphia, Pa.

A Symposium on Amino Acid Metabolism. Sponsored by the McCollum-Pratt Institute of The Johns Hopkins University. Edited by WILLIAM D. MCELROY AND H. BENTLEY GLASS. 1048 pp., $12.50. The Johns Hopkins Press, Baltimore, Md.